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# A Systematic Evidence Map of Noncancer Health Endpoints and Exposures to Polychlorinated Biphenyl (PCB) Mixtures

**Office of Research and Development**
Center for Public Health & Environmental Assessment

*EPA/600/R-22/201F*

# A Systematic Evidence Map of Noncancer Health Endpoints and Exposures to Polychlorinated Biphenyl (PCB) Mixtures

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Center for Public Health and Environmental Assessment
Office of Research and Development
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# ABBREVIATIONS

| | |
|---|---|
| ACTH | adrenocorticotropic hormone |
| ALT | alanine aminotransferase |
| AOP | adverse outcome pathway |
| AhR | aryl hydrocarbon receptor |
| AST | aspartate aminotransferase |
| ATSDR | Agency for Toxic Substances and Disease Registry |
| BUN | blood urea nitrogen |
| BW | body weight |
| CASRN | Chemical Abstracts Service registry number |
| CERCH | Center for Environmental Research and Children's Health |
| CNS | central nervous system |
| CPAD | Chemical and Pollutant Assessment Division |
| CPHEA | Center for Public Health and Environmental Assessment |
| CYP450 | cytochrome P450 CYP1A2 |
| DoCTER | Document Classification and Topic Extraction Resource |
| EPA | Environmental Protection Agency |
| EPM | elevated plus maze |
| EZM | elevated zero maze |
| FVC | forced vital capacity |
| FEV1 | forceful exhalation |
| GGT | gamma-glutamyltransferase |
| GSH | glutathione |
| HAWC | Health Assessment Workspace Collaborative |
| HDL | low high-density lipoprotein |
| HERO | Health and Environmental Research Online |
| HF | heart failure |
| HPA | hypothalamus-pituitary-adrenal |
| HPT | hypothalamus-pituitary-thyroid |
| IGT | impaired glucose tolerance |
| i.p. | intraperitoneal |
| IR | insulin resistance |
| i.v. | intravenous |
| IARC | International Agency for Research on Cancer |
| IHD | ischemic heart disease |
| IRIS | Integrated Risk Information System |
| MCH | mean corpuscular hemoglobin |
| MCV | mean corpuscular volume |
| ML | machine learning |
| MetS | metabolic syndrome |
| MOA | mode of action |
| MI | myocardial infarction |
| NCI | National Cancer Institute |
| NHANES | National Health and Nutrition Examination Survey |
| NK | natural killer cells |
| NLP | natural language processing |
| NTP | National Toxicology Program |
| ORD | Office of Research and Development |
| OW/OB | overweight/obesity |
| PCBs | polychlorinated biphenyls |
| PCDFs | polychlorinated dibenzofurans |
| PECO | populations, exposures, comparators, and outcomes |
| PK | pharmacokinetic |
| QA | Quality Assurance |
| QAPP | Quality Assurance Project Plan |
| RBCs | red blood cells |
| SD | standard deviation |
| SE | standard error |
| SEMs | systematic evidence maps |
| SGOT | serum glutamic oxaloacetic transaminase, also known as AST |
| SGPT | serum glutamic pyruvic transaminase, also known as ALT |
| TCDD | 2,3,7,8-tetrachlorodibenzo-p-dioxin |
| TK | toxicokinetics |
| TSCATS | Toxic Substances Control Act Test Submissions |
| TSH | thyroid stimulating hormone |
| T4 | thyroxine |
| T3 | triiodothyronine |
| WOS | Web of Science |

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# EXECUTIVE SUMMARY

Assessing health outcomes associated with exposure to polychlorinated biphenyls (PCBs) is important given their persistent and ubiquitous nature. PCBs are classified as a Group 1 carcinogen, but the full range of noncancer health effects that could result from exposure to PCBs has not been systematically summarized and evaluated. This review compiles and organizes human and other mammalian studies of noncancer health endpoints measured with exposure to PCB mixtures to identify areas of robust research, as well as areas of uncertainty and research needs.

A protocol was developed that describes the systematic review methods, including the literature search strategy and the Populations, Exposures, Comparators, and Outcomes (PECO) criteria used to facilitate subsequent screening and categorization of literature into a systematic evidence map of PCB exposure and noncancer health endpoints across 15 organs/systems. A comprehensive literature search yielded 62,599 records. After a prioritization step that included machine learning and natural language processing, 17,037 studies were manually screened at the title and abstract level. An additional 900 studies identified by experts or supplemental searches were also included, for a total of 17,937 studies reviewed. After full-text screening of 3,889 references, 1,586 studies met PECO and were included in the database. Relevant study details such as the PCB congeners measured or administered, organs/systems and endpoints assessed, exposure duration, and species were extracted into literature summary tables. Summary data are available online as interactive visuals with downloadable metadata.

We identified 637 mammalian toxicological studies evaluating endpoints in a variety of species exposed for different durations and at different life stages and 953 epidemiological studies conducted among diverse populations. Although human and other mammalian data are abundant for some organs/systems (e.g., hepatobiliary, nervous system, and reproductive), other endpoints of great public interest (e.g., cardiovascular disease, autism) have not been extensively studied in the context of exposure to PCB mixtures. Furthermore, despite many years of research, sparse data exist for inhalation and dermal exposures, which are highly relevant human exposure routes. Robust research is available to inform PCB hazard assessments for most organs/systems, but the amount of data to inform associations with specific endpoints differs. This evidence map provides a foundation for future systematic reviews and noncancer hazard assessments of PCB mixtures and for strategic planning of research to address areas of greater uncertainty.

# 1. INTRODUCTION

Polychlorinated biphenyls (PCBs) are halogenated organic pollutants consisting of 209 congeners varying in the number and position of chlorine atoms substituted on biphenyl rings. PCBs were produced as technical mixtures (e.g., Aroclors) containing numerous individual congeners. Mixtures of these congeners were used as dielectric fluids in capacitors and transformers, as lubricants, and as additives in a variety of other products, including paints and caulk. PCB production was banned in the United States in 1979 (U.S. EPA, 1979) and in most of the world by the time the Stockholm Convention was adopted in 2001 (SCPOP, 2008). Even so, because of their widespread use, disposal, and resistance to degradation, these chemicals are pervasive in the environment and biota.

Humans are exposed to PCBs throughout their lifetimes, including prenatally and during the early postnatal period through breastfeeding (van den Berg et al., 2017), with continuing exposure through multiple routes including diet and inhalation (Weitekamp et al., 2021). Occupational exposure historically occurred during production or use of PCBs and PCB containing products (Wolff, 1985), and may still occur, for example through maintenance, repair, or recycling of old PCB containing products or disturbance of construction materials containing PCBs (Okeme and Arrandale, 2019; Herrick et al., 2007). The general population can be exposed to PCBs by ingesting contaminated food (especially fish from contaminated waters), and by inhaling contaminated air, in both indoor and outdoor settings, especially at locations which still use electrical equipment and/or building and construction products containing PCBs. The issue of potential inhalation exposure to PCBs in contaminated buildings, including some schools, is an environmental health topic that has received much attention from the US Environmental Protection Agency (U.S. EPA, 2019, 2015, 2012).

The PCB mixtures associated with each exposure pathway differ from each other and from the original technical mixtures due to differential degradation of the individual congeners in the environment over time, variable partitioning of PCB congeners in environmental compartments, and differences in toxicokinetics. Another factor contributing to differences between modern environmental PCB mixtures and technical mixtures is the ongoing, inadvertent PCB production that occurs during certain manufacturing processes, such as pigment production (Zhao et al., 2020a; Vorkamp, 2015; Hu and Hornbuckle, 2010). Therefore, humans are exposed to different environmental mixtures of PCBs from different sources (Ampleman et al., 2015; Hornbuckle and Robertson, 2010) that have distinct congener compositions from the original produced mixtures. Furthermore, the composition of an exogenous environmental PCB mixture is subject to change after uptake into the human body as different congeners are metabolized and eliminated at different rates. Consequently, relating measures of PCB congeners in biological matrices to their

corresponding environmental source mixtures can be challenging, which complicates traditional risk assessment (Christensen et al., 2021).

Associations between PCB exposure and cancer and noncancer health endpoints have been reported in both human epidemiological and experimental animal studies (IARC, 2015; ATSDR, 2000). Of the 209 congeners, approximately 12 are considered "dioxin like," meaning that they bind to the aryl hydrocarbon receptor (AhR) and can interact with biological systems through the same mode of action as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (van den Berg et al., 2006; Poland et al., 1976). The remaining "nondioxin-like" congeners have also been reported to be associated with health endpoints; however, the specific hazards, dose-response relationships, and modes of action are variable and not as clearly understood for these PCBs. National and international health agencies have assessed PCB toxicity, including cancer (IARC, 2015; U.S. EPA, 1996) and noncancer endpoints (ATSDR, 2000; U.S. EPA, 1994, 1993). The International Agency for Research on Cancer (IARC) has classified PCBs as Group 1 carcinogens (IARC, 2015). However, the most comprehensive review of the potential effects of PCB exposure to date was conducted by the Agency for Toxic Substances and Disease Registry (ATSDR) (ATSDR, 2011, 2000). These reviews identified several noncancer outcomes sensitive to PCB exposure, including dermal, ocular, immune, thyroid, liver, reproductive, developmental, and neurodevelopmental effects (ATSDR, 2000). New research since ATSDR's assessments suggests the potential for additional health hazards, notably metabolic and cardiovascular effects. Furthermore, the full database of PCB literature has not previously been reviewed using systematic methods with the intent to identify most of the available data informing potential noncancer health hazards of exposure to PCB mixtures.

Systematic evidence maps (SEMs) are a useful tool to gain appreciation for the size and content of a literature database (Thayer et al., 2022). SEMs are used as analysis tools, which "do not seek to synthesize evidence but instead to catalog it, utilizing systematic search and selection strategies to produce searchable databases of studies along with detailed descriptive information" (Elsevier, 2017). In this approach, systematic review methods are used, including a targeted search of the literature guided by Populations, Exposures, Comparators, and Outcomes (PECO) criteria (see Table 1) and subsequent study categorization and development of visualizations to "map" the contents of the database. The resulting map can be used to evaluate the data available to inform specific questions that could be of interest for future systematic reviews.

**Table 1. Populations, exposures, comparators, outcomes (PECO) criteria[a]**

| PECO element | Description of Studies Included |
|---|---|
| **Populations** | **Human:** Adults and/or children with exposure to PCBs at any life stage.<br><br>**Animal**: Nonhuman mammalian animal species (whole organism) exposed during any life stage (during any period from in utero through adulthood). Studies including evaluations of transgenic animals only (i.e., with no evaluations of exposure-response relationships in wild-type animals) were considered "Potentially Relevant Supplemental Material." |
| **Exposures** | **Human**: Any exposure to PCBs (in vivo) as determined by controlled exposure, measured PCB concentration in contact medium (e.g., food, air, dust), biomarkers of exposure (e.g., serum PCB levels), or occupation in a job involving exposure to PCBs (e.g., electric capacitor manufacturing). The following exposure assessment methods/exposure contexts were considered "Potentially Relevant Supplemental Material" in the absence of biomarker measurements or estimates derived using scientifically sound methods: Yusho/Yu-Cheng patient status; consumption of fish (or marine mammals or other wildlife); and residential proximity to a PCB-contaminated site.<br><br>**Animal:** One or more oral (gavage, diet, drinking water, intragastric), inhalation (aerosol, vapor, or particle; whole-body or nose-only), dermal (occlusive, semiocclusive, nonocclusive), or injected (intravenous, subcutaneous, intraperitoneal) treatment(s) with any clearly quantified dosage of PCB congeners or PCB mixtures administered to a whole animal (in vivo).<br><br>*Studies were considered "Potentially Relevant Supplemental Material" if they used only routes of administration not listed above (e.g., intratracheal instillation, intracisternal injection) or evaluated only combinations of PCBs with other exposures (e.g., metals).* |
| **Comparators** | **Human:** A referent or comparison population that is unexposed or exposed at lower levels of PCBs, or exposed to PCBs for shorter periods of time, or cases versus controls, or a repeated measures design. However, worker surveillance studies are considered to meet PECO criteria even if no statistical analysis using a referent group is presented. Case reports and case series were considered "Potentially Relevant Supplemental Material."<br><br>**Animal:** A concurrent control group exposed to vehicle-only treatment or untreated control. |
| **Outcomes** | **Human**: Any examination of survival, body weight, or development, or of the structure or function of dermatological, cardiovascular, endocrine, gastrointestinal, hematological, hepatobiliary, immune, nervous, ocular, musculoskeletal, urinary, respiratory, or reproductive cells, tissues, or systems.<br><br>**Animal**: Any examination of survival, body weight, or development, or of the structure or function of dermatological, cardiovascular, endocrine, gastrointestinal, hematological, hepatobiliary, immune, nervous, ocular, musculoskeletal, urinary, respiratory, or reproductive cells, tissues, or systems.<br><br>*In general, endpoints related to clinical diagnostic criteria, disease outcomes, histopathological examination, or other apical/phenotypic outcomes are considered to meet PECO criteria and are prioritized for evidence synthesis while endpoints such as observations of cellular structure, gene expression, cell signaling, or other similar biochemical measures are considered "Potentially Relevant Supplemental Material."* |

[a]PECO criteria are based on those presented in U.S. EPA (2019).

This evidence map's main objective is to summarize available noncancer health endpoint data for mammalian toxicological and human epidemiological studies of exposures to PCB mixtures. By identifying health endpoints with databases sufficient to support evaluations of coherence across evidence streams (i.e., from studies in humans and nonhuman mammals) and across biologically related endpoints (e.g., endpoints linked through a common adverse outcome pathway), we can highlight the databases with the highest likelihood of supporting an analysis of causal relationships with exposure to PCB mixtures for future systematic reviews. Conversely, by identifying areas with poorer databases, this evidence map can also be used to inform future research efforts on topics that have been insufficiently studied.

# 2. METHODS

## 2.1. LITERATURE SEARCH

A protocol was developed that describes the literature search strategy and PECO criteria used to facilitate subsequent screening and categorization of literature into a SEM of PCB exposure and noncancer health endpoints (U.S. EPA, 2019). The protocol was registered in 2019 via Zenodo (https://doi.org/10.5281/zenodo.3585771). Peer-reviewed literature was identified by searching PubMed (National Library of Medicine), Web of Science (Clarivate Analytics), and, prior to 2019, Toxline (National Library of Medicine). The literature search strategy relied on terms describing PCB mixtures and individual congeners (e.g., "polychlorinated biphenyls," "Aroclor," "PCB," "tetrachlorobiphenyl") to gather information on exposure to the chemicals of interest. Additional exposure terms were used to identify studies not indexed by the chemical name (e.g., "capacitor manufacturing workers," "Yu-Cheng," "New York State Angler Cohort"). These search terms were intentionally broad and did not prioritize studies in which exposure was quantified for individual participants; this was considered during screening of the literature. The detailed search strategies are presented in Table S1A, and a summary of search results is provided in Table S1B in Supplementary File 1. A list of all references retrieved through the literature searches is provided in Supplementary File 2, and search results by year are provided in Supplementary Files 3–9. The original search, conducted in 2015, was not restricted by publication date or language (Supplementary File 3). Literature search updates were conducted yearly through September 1, 2021 and were restricted to the 12-month period since the original search or the most recent update (Supplementary Files 4–9). Each annual search update utilized the same search terms. Records identified through the original literature search were prioritized electronically as described below. Reference lists of health assessments published by federal, state, and international health agencies were searched to identify seed references (described below), but additional supplemental search strategies (e.g., citation mapping) were not applied. Twenty-five references were identified through recommendation by technical experts (see Table S1C).

## 2.2. ELECTRONIC APPROACHES USED TO REFINE A LARGE DATABASE

Screening a large number of candidate studies for inclusion is time-consuming when conducted manually by human reviewers. Automation tools are available to reduce the human effort needed for screening. For this review, natural language processing (NLP) and machine learning (ML) techniques were employed to identify the most relevant literature for manual screening. Studies were prioritized using DoCTER, a Document Classification and Topic Extraction Resource (Varghese et al., 2018). Details of the NLP and ML methods are described elsewhere

(Varghese et al., 2019; Varghese et al., 2018). Briefly, 483 studies selected as having met the PECO criteria for inclusion in this review (see Table 1) were designated as seed references (provided in Table S1D). Seed references are a set of relevant documents that are labeled and included in the larger collection of unclassified documents. Seed references function as tracers in the document prioritization process, helping identify documents with similar content. For this review, seed references were identified during problem formulation (U.S. EPA, 2015), which was largely on the basis of a survey of references cited in health assessments published by federal, state, and international health agencies, most notably ATSDR (2000). Seed studies were included in the corpus of references identified by keyword searches and used to prioritize studies using an ML method called supervised clustering. In Phase 1 of a two-phased prioritization approach, titles and abstracts of all references identified by keyword searches, along with the seed references, were represented as a mathematical matrix using an NLP transformation and then organized into groups of references with semantic similarity (i.e., "clusters") using algorithms as depicted in Figure 1A. Two clustering algorithms (k-means, nonnegative matrix factorization) were applied using cluster sizes of 10, 20, or 30 references for a total of 6 different clustering approaches. Reference clusters that included seed references were identified as illustrated in Figure 1B.

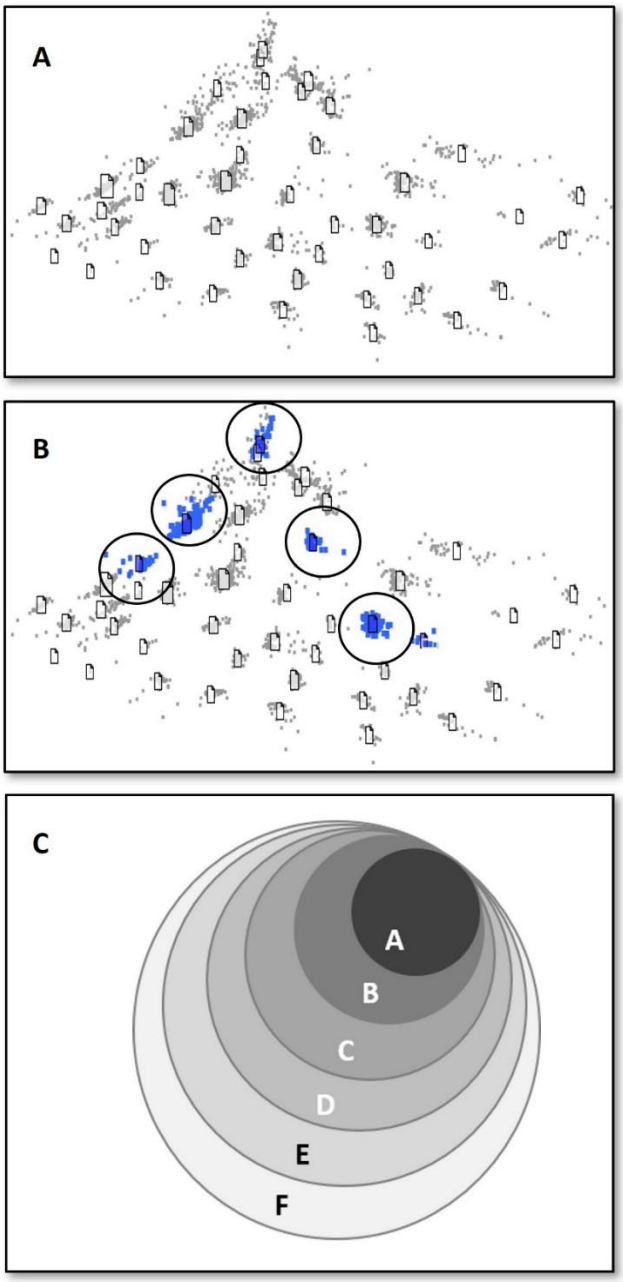


**Figure 1. Illustration of electronic prioritization approaches.**

1A. Schematic illustration of electronic prioritization of literature depicting references clustered by similarity using natural language processing. 1B. Illustration depicting clusters containing relevant seed references (circled blue clusters). Clusters were ranked by the number of seed studies included. 1C. Visualization of identified clusters. Clusters were organized into groups (A–F) on the basis of the number of approaches that identified the cluster such that Group A contains clusters that include seed references identified by six approaches and Group F contains clusters that include seed references identified by a single approach. All references in the top four groups (A–D) were manually screened for inclusion based on PECO criteria. Low scoring groups (E, F) were subjected to additional machine learning approaches to capture relevant references for manual screening.

In each of these six approaches, clusters were ranked in decreasing order of the number of seed studies included in the cluster, and clusters were accepted in order until 90% of the total set of seed studies was captured. A 90% threshold was selected because it provided an optimal balance between the statistical measures of recall (fraction of relevant studies retrieved) and precision (fraction of relevant studies among the retrieved studies) (Varghese et al., 2018). Higher thresholds would have resulted in diminished precision and a considerably higher manual screening burden given the size of the original literature database. This method was repeated for all six clustering approaches; thus, a given study could have appeared in one of the accepted clusters (and thus appear with the greatest fraction of the seed studies) in anywhere from zero to six of the approaches. Clusters containing seed references were grouped by the number of approaches in which they were identified (Groups A–F, Figure 1C). Studies that appeared in groups A–D (representing 6, 5, 4, or 3 approaches, Figure 1C) were subjected to manual title and abstract-level screening, as described in Section 2.3.1. Screened studies from Phase 1 were used to train the ML model in Phase 2.

In Phase 2, a supervised ML algorithm (support vector machines; (Varghese et al., 2018)) was used to predict relevance for those studies in the remaining groups of clusters that appeared in one or two approaches (groups E and F, Figure 1C). Also included in this approach was one group of studies excluded from initial clustering until abstracts were recovered and a second group of studies with titles only. The training data set for this secondary analysis is distinct from the seed references mentioned above and included all studies manually screened in Phase 1; the training data set for supervised ML thus included examples of studies that met PECO and those that did not. Studies predicted to be relevant in Phase 2 by the supervised ML algorithm were subjected to manual title and abstract-level screening. Details of the DoCTER prioritization strategy are presented in Table S1E, and a list of studies prioritized using DoCTER supervised clustering and ML approaches is provided in Table S1F.

Because fewer references were identified in yearly search updates, alternative approaches were used to prioritize the literature for screening (summarized in Figure 2). References identified in 2016 were directly subjected to manual screening without electronic prioritization. References identified after August 2016 were prioritized using SWIFT-Active Screener (Sciome, 2023), a web-based software application integrated with electronic prioritization using ML and statistical approaches. For each literature update, manually reviewed studies were used to train the model, which is updated iteratively, thus reducing manual screening efforts (Howard et al., 2020).

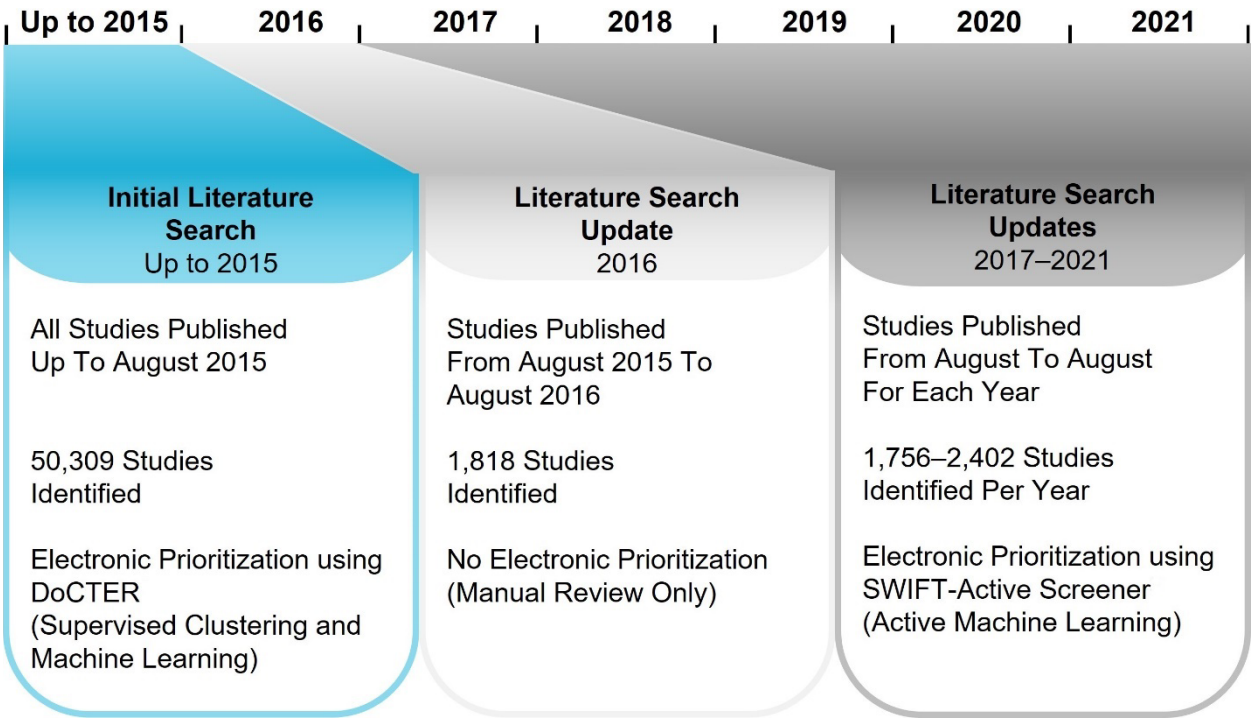


**Figure 2. Chronology of prioritization approaches applied to PCB literature search results.**

The initial 2015 literature search used DoCTER, an electronic prioritization approach described in Section 2.2 and in ICF (2021). The literature updates from 2017–2021 utilized SWIFT-Active Screener, another electronic prioritization program fully described in Sciome (2023).

## 2.3. LITERATURE SCREENING

### 2.3.1. Title and Abstract Screening of the Literature

Prioritized records were combined with smaller groups of records, including seed references, records identified through literature search updates, and references suggested by technical experts, into a single database. The literature was then manually screened in two steps to determine whether individual studies should be included or excluded as a primary source of health endpoint data based on PECO criteria shown in Table 1. Step 1 consisted of title and abstract screening, while Step 2 involved full-text screening (Section 2.3.2).

In Step 1, two trained screeners independently conducted a manual title and abstract review using structured forms developed in DRAGON (a modular database with integrated screening and literature evaluation tools developed for systematic review) (ICF, 2018) to identify records that appeared to meet the PECO criteria. For citations with no abstract, articles were screened based on title relevance. Screening conflicts were resolved by a third reviewer. Each study was categorized to one of the following bins: "Relevant to Hazard Identification in Humans", "Relevant to Hazard Identification in Animals" (nonhuman mammals only), "Potentially Relevant

Supplemental Material", or "Not Relevant". Identification of studies "Relevant to Hazard Identification in Humans" or "Relevant to Hazard Identification in Animals" was based on the species of the population(s) exposed to PCBs. Studies identified as "Not Relevant" did not meet PECO. "Potentially Relevant Supplemental Material" included toxicokinetic studies, studies describing pharmacokinetic models for PCB congeners and mixtures, and mechanistic studies. Additional records tracked as "Potentially Relevant Supplemental Material" included conference abstracts, secondary data sources (e.g., reviews, agency assessments), non-English-language studies, exposure studies unrelated to health endpoints, and human case reports or case series. The tags used for study categorization are summarized in Tables S1G, S1H, and S1I. Categories of "Potentially Relevant Supplemental Material" are shown in Table S1I.

References retrieved through August 2016 were screened and tagged using DRAGON. Screening decisions and study metadata recorded in DRAGON (v. 03-25-2016) were recently moved to a second generation, web-based systematic review platform rebranded as litstream™ (ICF, 2021). References identified in search updates after August 2016 were screened in SWIFT-Active Screener until the software indicated a likelihood of 95% that all relevant studies had been captured. This threshold is comparable to human error rates (Bannach-Brown et al., 2018; Howard et al., 2016; Cohen et al., 2006) and is used as a metric to evaluate ML performance. A summary of literature prioritized using SWIFT-Active Screener is provided in Table S1J.

To validate the application of clustering and ML algorithms, a subset of nonprioritized studies was also randomly selected for manual title and abstract-level review.

### 2.3.2. Full-Text Screening of the Literature

Records not excluded or considered "Potentially Relevant Supplemental Material" based on the title and abstract advanced to full-text manual review using litstream. Full-text copies of these potentially relevant records were retrieved and independently assessed by two screeners to confirm eligibility according to the PECO criteria. Screening conflicts were resolved by a third reviewer. Seed references, which had been identified as meeting PECO during problem formulation (U.S. EPA, 2015) were also included in the full-text screen to categorize these records.

In addition to confirming that studies met PECO criteria, the health endpoints investigated in each study were identified using structured forms in litstream. Health endpoints were organized into the following categories based on Thayer et al. (2022): Cardiovascular, Dermal, Developmental, Endocrine, Gastrointestinal, Hematopoietic, Hepatobiliary, Immune System, Metabolic, Musculoskeletal, Nervous System, Ocular, Reproductive, Respiratory, and Urinary System. These organ/system categories were chosen because of their potential to include specific noncancer health endpoints that could be affected by PCB exposure at levels relevant to those experienced in the general population. Assignment of specific endpoints into each of the organs/systems was made by one or more coauthors based on their primary areas of expertise. Some studies evaluated multiple endpoints and so were assigned to multiple organs/systems. We recognize that there is crosstalk among many physiological systems, which can complicate the categorization of endpoints;

specific information on which endpoints are included in each organ/system is provided in Section 3.3. Studies focused entirely on cancer or frank toxicity, including mortality of unknown cause, and wasting, although not the focus of this review, were considered "Potentially Relevant Supplemental Material". Humans tend to be exposed to complex PCB mixtures that contain many congeners of varied toxic potency and potential modes of action (U.S. EPA, 2015). Since the focus of this review is on studies of mixtures that better reflect a typical human exposure scenario, toxicological 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".

Based on the results for the full-text review, summary-level, sortable lists of relevant literature were created for human and animal (nonhuman mammalian) studies for each organ/system. Fundamental study design information (e.g., study population, exposure assessment/design, PCB mixtures administered in nonhuman mammalian studies, health endpoints evaluated) was extracted for each study in Microsoft Excel by one individual and independently reviewed by at least one additional individual.

# 3. RESULTS AND DISCUSSION

## 3.1. LITERATURE SEARCH AND SCREEN

### 3.1.1. Literature Searches (2015–2021)

The results of the literature searches and screens for literature published through August 31, 2021, are summarized in the Literature Flow Diagram presented in Figure 3. After duplicate removal, 50,309 studies were identified from the initial literature search conducted in 2015. Yearly literature search updates were conducted from 2016 to 2021, yielding between 1,756 and 2,402 unique studies per year, which added 11,390 studies. Thus, 61,699 studies were identified after duplicate removal.

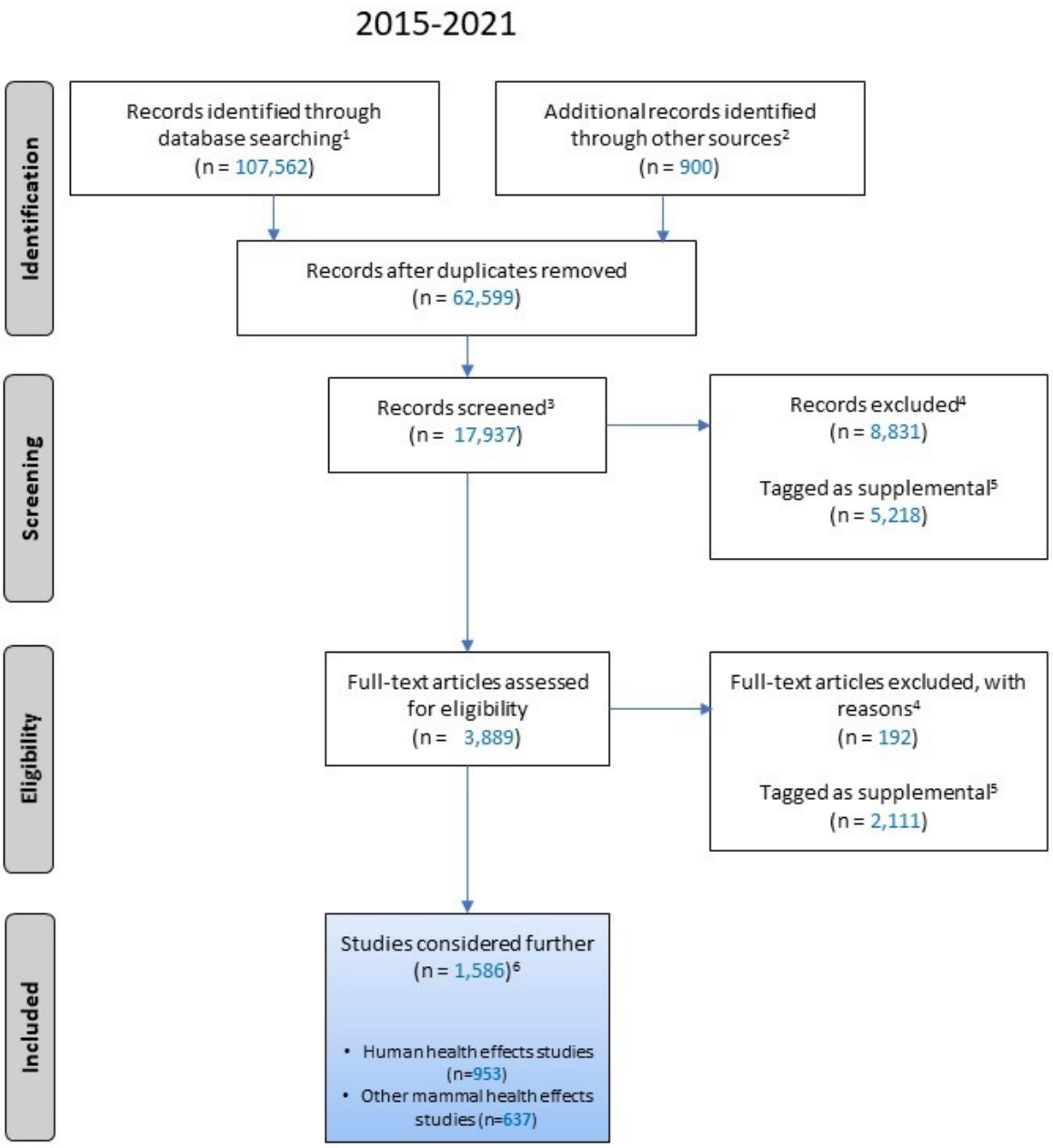


**Figure 3. Literature search flow diagram for PCBs.**

[1]Searches were conducted up to August 31, 2021, in PubMed, Web of Science, and, prior to 2019, also Toxline.
[2]References were identified by technical experts or through supplemental searches, including seed references.
[3]Records were prioritized for screening using machine learning tools (DoCTER for references identified in 2015–2016 database searches and SWIFT-Active Screener for 2017–2021).
[4] Studies not meeting PECO criteria.
[5] "Potentially Relevant Supplemental Material" includes conference abstracts, reviews, and non-English studies that met PECO and studies on PECO-related topics (e.g., toxicokinetic or mechanistic studies).
[6]Four studies examined health endpoints in both humans and other mammals.

### 3.1.2. Electronic Prioritization for Manual Review

Manual screening of the entire database was time and cost prohibitive because of the vast number of studies. Therefore, electronic prioritization approaches were implemented to identify studies most likely to meet the PECO criteria (see Table 1). Results and prioritization strategies are summarized in Figure 2 and Table S1B.

As described above for the initial literature search conducted in 2015, both supervised clustering and ML approaches were used to prioritize studies for manual screening. The number of studies identified using electronic prioritization methods is summarized in Table 2.

**Table 2. Electronic prioritization of literature for hazard identification**

| Study group[a] | Prioritization approach | Number of prioritized studies |
|---|---|---|
| **2015 literature search (original search): 50,309 records retrieved – DoCTER Prioritization** | | |
| Groups A–D (see Figure 1C) | DoCTER – Supervised Clustering | 4,605 |
| Groups E–F (see Figure 1C) | DoCTER – Supervised Clustering and ML | 3,363 |
| Studies with titles only | DoCTER – ML | 3,209 |
| **Total number electronically prioritized – DoCTER** | | **11,177** |
| **2017–2021 literature search updates** | | |
| 2017<br>2018<br>2019<br>2020<br>2021 | SWIFT-Active Screener – Active ML | 609<br>819<br>855<br>917<br>842 |
| **Total number electronically prioritized – Active ML** | | **4,042** |

[a]As described in Section 2.2, titles and abstracts were organized into clusters based on semantic similarity using six different approaches. Clusters were ranked by the number of seed studies included in each and organized into groups (A–F) on the basis of the number of approaches that identified the cluster; Group A contains clusters that include seed references identified by six approaches, and Group F contains clusters that include seed references identified by a single approach. All references in Groups A–D were manually screened; Groups E and F were subjected to additional machine learning approaches to prioritize references for manual screening. The bold numbers are defined as "Total number electronically prioritized – Active ML".

Studies not manually reviewed included those not identified by any of the clustering approaches or those identified by one or two approaches and predicted not to be relevant during the ML phase. Collectively, clustering and ML approaches using DoCTER identified 11,177 studies from the initial literature search conducted in 2015 as high priority studies for manual review. Review of a randomly selected subset of nonprioritized studies demonstrated that less than 10% of nonprioritized studies were relevant based on PECO criteria, indicating that these approaches captured at least 90% of the literature relevant to informing associations between PCB exposure and health endpoints. In 2016, all 1,818 unique studies were manually reviewed. Of the 9,572

studies retrieved in 2017–2021, 4,042 studies were prioritized using SWIFT-Active Screener and were manually screened. Thus, 17,037 (27.6%) of the 61,699 studies retrieved through literature searches were manually reviewed.

### 3.1.3. Literature Screening

In addition to electronically prioritized studies, 900 other studies were manually reviewed. These included 483 seed references (see Table S1D) and 417 studies identified by technical experts or through supplemental literature searches conducted to identify information on PCB toxicokinetics or modes of action (see Tables S1C and S1K). The manual review thus included 17,937 studies. Of these, 3,889 were identified as potentially relevant and subjected to full-text review and categorization by health endpoint. After full-text review and categorization, 1,586 studies were included in literature summary tables organized by organ/system, with one summary table per system for human studies and a second for animal studies (nonhuman mammals only). A total of 953 human studies and 637 nonhuman mammalian studies were evaluated for health endpoints and exposure to PCBs.

Most studies evaluated more than one type of health endpoint, so the numbers of studies for each system are not expected to sum to the total number of studies, nor are the numbers of studies of each health endpoint expected to sum to the total number of studies for the relevant organ/system. Furthermore, sometimes results from a single research project are reported in multiple publications. Different publications might focus on different subsets of data, use different statistical or other analytical approaches, or update results published from earlier stages of data collection. For example, a study of women with and without endometriosis first described by Buck Louis et al. (2005) was later reanalyzed using different statistical techniques (Roy et al., 2012; Gennings et al., 2010). When the same results were reported in multiple publications or when some publications reported results based on less complete data, we considered those data only as reported in the most up-to-date or most complete publication. Even so, this multiplicity of published reports is important to note when interpreting numbers of studies identified by the literature search and screening process and evaluation of the adequacy of the database to support hazard conclusions. To help readers navigate through the literature and understand the basis for our study counts, we have developed interactive visualizations that allow for identification of the individual references included for each organ/system (https://hawcprd.epa.gov/summary/assessment/100500282/visuals/; underlying data provided in Table S1L). These visualizations can also be used to filter references by study design characteristics of interest to generate customized reference lists and counts of studies that we do not include in this report.

## 3.2. GENERAL CONSIDERATIONS

One potential use for this evidence map is to provide a starting point for future health hazard assessments of PCB mixtures. Such assessments could include full systematic reviews of the evidence for PCB effects on specific types of health outcomes. Because of the time and level of effort required to develop a full systematic review, a practical preliminary step for prioritizing organs/systems for systematic review is to identify health endpoints with databases that are sufficiently large and informative to potentially support meaningful conclusions about causal relationships with PCB exposure. This evidence map is designed to facilitate the identification of such databases that could be further evaluated through subsequent systematic reviews, which would include study evaluation and evidence synthesis and integration (U.S. EPA, 2019). Determination of causal relationships between exposures and health effects forms the basis for hazard identification, which is a fundamental step in human health risk assessment (NRC, 1983). The following sections describing the databases for each organ/system include information on the types of considerations important for establishing an exposure hazard for that system. One consideration is the availability of information from human studies - while nonhuman mammalian data can be useful to support findings from human studies and can help address gaps in the human database (due, e.g., to the difficulty associated with measuring certain endpoints in humans), a lack of nonhuman mammalian studies is not considered a limitation if human data are sufficient to establish hazard. Other examples of considerations applicable for all organs/systems, described in the remainder of this section, include the following: the number of studies and endpoints examined; public health significance of the endpoints; exposure level, timing, and context; method of assessing exposure and health endpoints; and occurrence of co-exposures. Considerations that are most applicable for a specific organ/system are outlined in each organ/system summary section (e.g., validity and accuracy of a clinical diagnostic method for a certain health endpoint). For each organ/system, these factors were considered to develop conclusions regarding the potential for each database to support hazard identification.

Databases with the potential to inform coherence across biologically related endpoints are more likely to support strong hazard conclusions than databases including evaluations of only single endpoints in isolation. While a change in a single endpoint or biomarker of effect could be due to random chance, changes in several related endpoints are less likely to occur solely for this reason. In some instances, changes in multiple endpoints can indicate greater severity or progression along a disease continuum or provide more insight into possible mechanisms/modes of action. Therefore, throughout this review, information is often provided on the availability of studies evaluating multiple, biologically related endpoints.

Exposure timing is one important consideration for assessing the potential sensitivity of studies conducted in humans or other mammals. This is especially true for studies of potential effects on development. The developmental period is critical because it is the foundation for health throughout an organism's lifetime. Adverse effects on development can occur because of chemical

exposure during gestation, infancy, adolescence, or even early adulthood (e.g., the nervous system continues to develop until around age 21 years in humans) (Makris et al., 2008; Adams et al., 2000). For many endpoints, sensitive developmental windows can represent periods of important biological progressions. The exact developmental period of vulnerability varies for different endpoints, depending on the duration or timing of a given developmental process. The ability of a human exposure measurement to correctly classify individuals with respect to their exposure during an etiologically relevant period(s) will vary depending on the specific health endpoint, exposure context and timing of measurement, and study population. Evaluating exposure during the preconception, pregnancy, and perinatal periods presents unique challenges. For example, PCB body burden changes with changes in maternal weight and body composition during pregnancy and lactation; thus, the timing of sample collection is critical and should reflect an etiologically relevant period for the endpoint of interest [e.g., (Bloom et al., 2007)]. In addition, for many endpoints, critical or sensitive windows of exposure have not been well characterized. However, studies of exposures during those windows are important to optimize the sensitivity of the database for identifying effects on those endpoints. Specific windows of susceptibility and the existence of studies that evaluate exposures during those windows are discussed in the summary sections for each organ/system.

### 3.2.1. Human Studies

Assessment of methodological features such as the study population, study design, exposure and endpoint measurement, analytical methods, and completeness of reporting guide the evaluation of human studies with respect to their validity and utility for assessing relationships between health effects and chemical exposures. The most informative studies include an appropriate sample of the target population (e.g., representative and of adequate size for the study question), use sensitive and specific methods to assign exposure status and to measure health endpoints, and use appropriate statistical techniques and design considerations to minimize potential bias and confounding. For epidemiological studies, some general considerations apply across all exposure types and organs/systems (U.S. EPA, 2022); some specific examples particularly relevant to the database of PCB studies are outlined here.

In terms of study population, general population samples might enable examination of health endpoints observed at relatively lower levels of exposure compared with persons exposed occupationally or through specific high-exposure events with relevant coexposures. Conversely, occupational studies can provide valuable information regarding certain exposure contexts that are not otherwise observed in epidemiology studies, such as high-level exposure or exposure via inhalation or dermal routes, and thus can be useful for informing hazard when considered together with other sources of evidence. In the PCB database, many studies have evaluated health endpoints occurring among persons accidentally exposed to PCBs and their combustion by-products, polychlorinated dibenzofurans (PCDFs) (Hutzinger et al., 1985), via contaminated rice bran oil, in the Yusho (Japan, 1968) and Yu-Cheng (Taiwan, 1979) incidents. As described by ATSDR (2000)

and Kunita et al. (1985), PCDFs and dioxin-like PCBs could affect the same health endpoints because they share a common mode of action mediated by the AhR. Such co-occurring exposures are generally present in epidemiological studies and can complicate evaluation of health endpoints if they are highly correlated with PCBs and the endpoint of interest in the study population. Other issues that need consideration in the Yusho/Yu-Cheng group of studies include the ability to define the exposed population (e.g., patient registries might be incomplete) and the magnitude of exposure (e.g., many studies rely on self-reported oil use, and often the lag between exposure and its measurement is considerable). Similar considerations of potential coexposures are important for interpreting and generalizing the results of studies in consumers of PCB-contaminated fish, marine mammals, or other wildlife. These dietary sources might contain PCBs in notable amounts, along with both other pollutants (e.g., methylmercury) and beneficial nutrients (e.g., long-chain fatty acids) (Paliwoda et al., 2016; Turyk et al., 2012). Throughout this review, information on the study population is considered in each database when determining the ability to generalize results to other populations with different exposure scenarios.

The most common types of study design for human studies of PCB exposure were cohort and cross sectional followed by case-control and other study designs. We note that while we designated study design using these broad categories for the purpose of this review, study design does not always fall cleanly into these bins. Prospective designs (e.g., cohorts or case-control studies nested within cohorts) are advantageous in that the temporality of the exposure preceding the outcome is ensured, in contrast to cross-sectional or typical case-control studies. For longer-lived PCB congeners, exposure measurements made concurrently with outcome ascertainment may adequately represent prior exposure status, but this is less certain for shorter-lived congeners (Christensen et al., 2021). However, cohort designs might not be efficient when evaluating rare health endpoints; in this case, other designs such as case-control studies are advantageous. As described above, several studies evaluate health endpoints following unintended exposure to PCBs and PCDFs in the Yusho and Yu-Cheng populations. Evaluation of these studies is complicated by the fact that membership in respective health registries is often used to confer "exposed" status, while measurements in biological tissues were taken at various time points after the exposure occurred, sometimes concurrent with the endpoint measure and sometimes before or afterward. For this review, studies of Yusho and Yu-Cheng are generally considered to be cohort studies, but specific cases are noted when exposure measures are interpreted differently based on timing relative to outcome ascertainment. Information on study design is considered in each database to help determine whether the data can inform presence of causal links (considering, e.g., temporality) between PCB exposure and evaluated endpoints.

Most human studies in the database characterized PCB exposure using measures of PCB congeners or their metabolites in biological matrices. The most reported measurements were made in plasma/serum collected from adults outside the context of pregnancy or lactation or, for studies of mother-infant pairs, in maternal plasma/serum, umbilical cord plasma/serum, human milk, or

child blood. PCB measurements in other tissues such as adipose tissue, placenta, or brain are much less common. PCBs are lipophilic, although the degree varies by congener and generally increases with increasing chlorination. This implies that the PCB content in lipid-rich tissues (such as milk) is substantially higher and possibly easier to detect and quantify compared with lipid-poor tissues (e.g., cord plasma/serum), especially in populations exposed to very low levels of PCBs. Throughout this review, exposure measurement methods are broadly considered when describing the database of human studies for each organ/system but would be evaluated in more detail at the study evaluation step of a full systematic review.

Outcome ascertainment methods vary across studies; endpoints can be measured using information from a variety of sources, including national databases (e.g., mortality data, cancer registries), medical records, pathology reports, self-report, assessment by study examiners, and biomarkers based on urine or blood samples. Suitability of the endpoint measure (including factors such as reliability and validity in different populations or periods) will depend on the specific health endpoint and study population. Many studies evaluate mortality rates, or cause-specific mortality rates, as a health endpoint. This is particularly common in the PCB literature for occupationally exposed populations. These estimates can provide valuable information when the cause-of-death coding is likely to be sensitive and specific, and when an appropriate comparator population is selected. Endpoint measurement methods are broadly considered when describing the database of human studies for each organ/system but would be evaluated in more detail at the study evaluation step of a full systematic review.

### 3.2.2. Nonhuman Mammalian Studies

Although using human data for risk assessment can reduce uncertainty, human data are often unavailable for reasons including the ethical implications of permitting human chemical exposures to reach levels associated with health effects. Therefore, laboratory animal studies are commonly conducted to investigate a range of endpoints useful for determining whether a chemical is likely to pose a hazard to human health (NRC, 1983). Evaluations of the utility of such studies for hazard identification might consider study design and experimental conduct, including features like reporting quality, internal validity, and study sensitivity (U.S. EPA, 2022). The most informative studies use accurate and valid methods to assess endpoints of interest and rely on appropriate statistical techniques and design considerations to limit potential bias (e.g., blinding, randomization, variable control) and to maximize sensitivity for detecting the endpoints of interest [e.g.,(Dishaw et al., 2020)].

Although human exposure to PCBs can occur through multiple routes, including dietary intake, inhalation, and dermal contact (Weitekamp et al., 2021), few mammalian data are available on health endpoints and inhalation and dermal exposures to PCBs. As described in (see Section 1), PCB inhalation in contaminated buildings has been an area of great public health interest, especially in the context of PCB exposure in schools (U.S. EPA, 2019, 2015, 2012). The scarcity of PCB data for inhalation exposure represents one important area of uncertainty for risk assessment (U.S. EPA,

2019; Lehmann et al., 2015; U.S. EPA, 2015). Pharmacokinetic modeling approaches offer potential utility for extrapolating dose-response data among exposure routes (Fairman et al., 2020); however, more research is needed to address the complexity and interactions of multiple PCB congeners with unique toxicokinetic behavior and exposure pathways. Throughout this review, information is provided on the routes of exposure addressed in the database for each organ/system to provide an indication of the ease with which study results can be applied to various human exposure scenarios.

## 3.3. ORGAN/SYSTEM DATABASE SUMMARIES

The available human and nonhuman mammalian studies for each organ/system will be reviewed in Sections 3.3.1 through 3.3.15. Overview figures summarizing study design information were generated from the interactive visualizations described in Section 3.1.3 (https://hawcprd.epa.gov/summary/assessment/100500282/visuals/) and will be referenced throughout this report; they are highlighted briefly here. Figure 4 presents an overview of human and nonhuman mammalian studies across the 15 organs/systems.

| | Evidence Stream | |
|---|---|---|
| Organ/System | Human | Other Mammal |
| Cardiovascular | 81 | 47 |
| Dermal | 34 | 52 |
| Developmental | 130 | 170 |
| Endocrine | 125 | 177 |
| Gastrointestinal | 24 | 57 |
| Hematopoietic | 46 | 61 |
| Hepatobiliary | 86 | 357 |
| Immune System | 105 | 131 |
| Metabolic | 197 | 69 |
| Musculoskeletal | 30 | 23 |
| Nervous System | 214 | 174 |
| Ocular | 18 | 27 |
| Reproductive | 227 | 218 |
| Respiratory | 30 | 49 |
| Urinary System | 29 | 104 |
| Grand Total | 953 | 637 |

Number of Studies

1 357

**Figure 4. Overview of Human and Other Mammalian Studies Across Organs/Systems**

Summary of the database of studies evaluating exposures to PCB mixtures and health endpoints organized by system. Lists of studies included in each count can be accessed via the online interactive version of this figure (https://hawc.epa.gov/summary/visual/assessment/100500282/OverviewAllStudies/). Shading intensity corresponds with the number of studies in each category, from 1 to 357, which is the maximum number of studies in any category.

For the human studies, the database is organized by organ/system and study population in Figure 5, by organ/system and study design in Figure 6, and by organ/system and PCB exposure metric in Figure 7. When describing exposure metrics, the term "blood" was used to broadly capture measurements made in whole blood or any fraction (serum or plasma). Multiple blood metrics are identified to indicate the lifestage represented by the measurement (i.e., blood (collected from adults outside the context of pregnancy or lactation), child blood, maternal blood, cord blood).

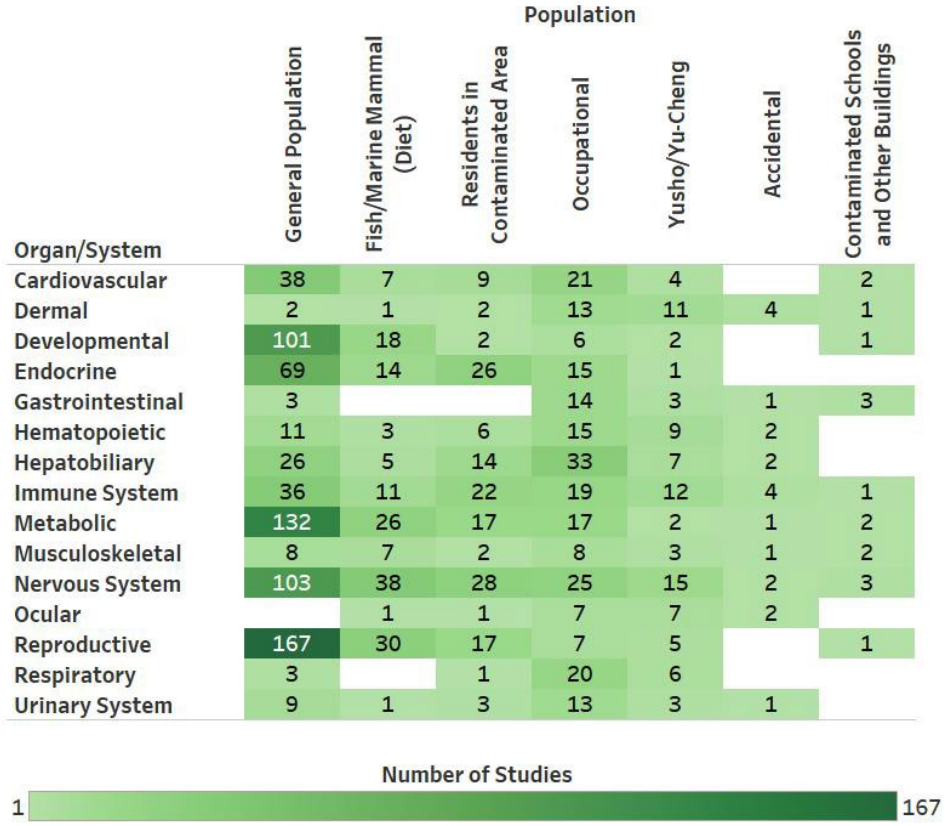


**Figure 5. Overview of Human Studies by Organ/System and Population**

Summary of the database of human studies evaluating exposures to PCB mixtures and health endpoints organized by system and population. Lists of studies included in each count can be accessed via the online interactive version of this figure (https://hawc.epa.gov/summary/visual/assessment/100500282/OverviewHumanStudies/). The online figure can be expanded to include information by endpoint category and can be filtered by organ/system (options: cardiovascular, dermal, developmental, endocrine, gastrointestinal, hematopoietic, hepatobiliary, immune system, metabolic, musculoskeletal, nervous system, ocular, reproductive, respiratory, urinary system), study design (options: case-control, cohort, cross-sectional, other), population (options: accidental, contaminated schools and other buildings, fish/marine mammal (diet), general population, occupational, residents in contaminated area, Yusho/Yu-Cheng), sex (relevant only for reproductive endpoints; options: couple, female, male), and exposure metric (options: adipose tissue, blood, breast milk, child blood, cord blood, dietary estimates, fish consumption, maternal blood, occupational/JEM, other metric [includes dust and modeled estimates], other tissue). Shading intensity corresponds with the number of studies in each category, from 1 to 167, which is the maximum number of studies in any category.

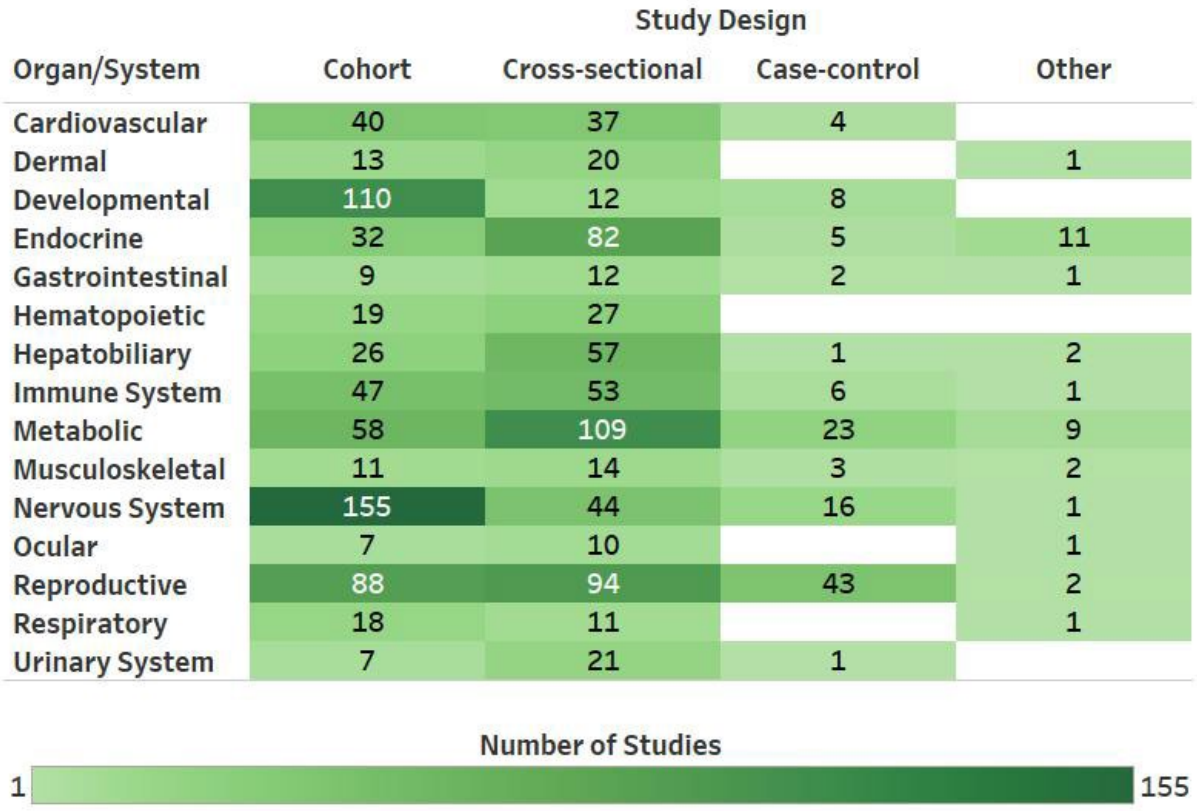


**Figure 6. Overview of Human Studies by Organ/System and Study Design**

Summary of the database of human studies evaluating exposures to PCB mixtures and health endpoints organized by system and study design. Lists of studies included in each count can be accessed via the online interactive version of this figure (https://hawc.epa.gov/summary/visual/assessment/100500282/OverviewHumanStudies/). The online figure can be expanded to include information by endpoint category and can be filtered by organ/system (options: cardiovascular, dermal, developmental, endocrine, gastrointestinal, hematopoietic, hepatobiliary, immune system, metabolic, musculoskeletal, nervous system, ocular, reproductive, respiratory, urinary system), study design (options: case-control, cohort, cross-sectional, other), population (options: accidental, contaminated schools and other buildings, fish/marine mammal (diet), general population, occupational, residents in contaminated area, Yusho/Yu-Cheng), sex (relevant only for reproductive endpoints; options: couple, female, male), and exposure metric (options: adipose tissue, blood, breast milk, child blood, cord blood, dietary estimates, fish consumption, maternal blood, occupational/JEM, other metric [includes dust and modeled estimates], other tissue). Shading intensity corresponds with the number of studies in each category, from 1 to 155, which is the maximum number of studies in any category. JEM = job exposure matrix.

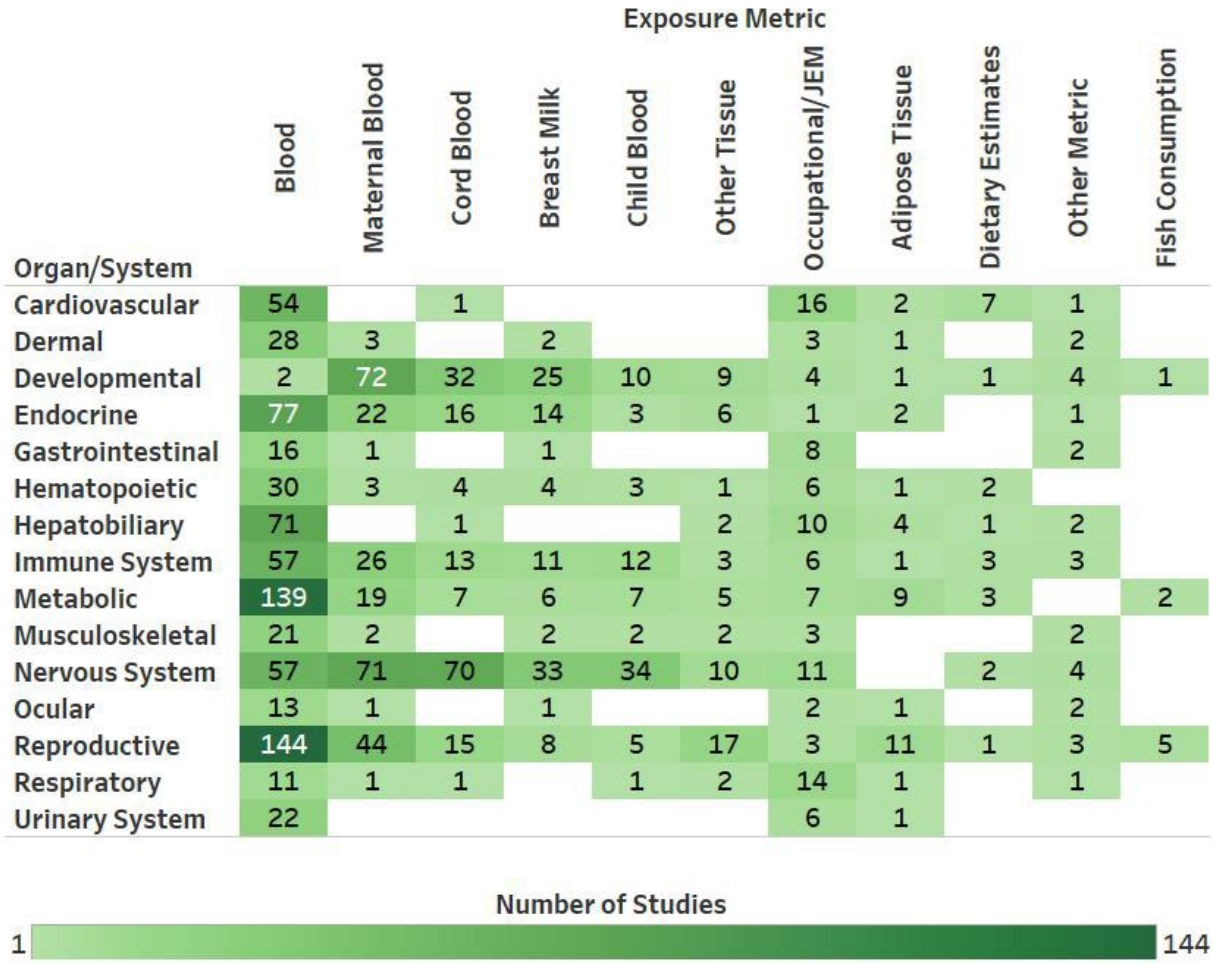


**Figure 7: Overview of Human Studies by Organ/System and Exposure Metric**

Summary of the database of human studies evaluating exposures to PCB mixtures and health endpoints organized by system and exposure metric. Lists of studies included in each count can be accessed via the online interactive version of this figure (https://hawc.epa.gov/summary/visual/assessment/100500282/OverviewHumanStudies/). The online figure can be expanded to include information by endpoint category and can be filtered by organ/system (options: cardiovascular, dermal, developmental, endocrine, gastrointestinal, hematopoietic, hepatobiliary, immune system, metabolic, musculoskeletal, nervous system, ocular, reproductive, respiratory, urinary system), study design (options: case-control, cohort, cross-sectional, other), population (options: accidental, contaminated schools and other buildings, fish/marine mammal (diet), general population, occupational, residents in contaminated area, Yusho/Yu-Cheng), sex (relevant only for reproductive endpoints; options: couple, female, male), and exposure metric (options: adipose tissue, blood, breast milk, child blood, cord blood, dietary estimates, fish consumption, maternal blood, occupational/JEM, other metric [includes dust and modeled estimates], other tissue). Shading intensity corresponds with the number of studies in each category, from 1 to 144, which is the maximum number of studies in any category. JEM = job exposure matrix.

For the nonhuman mammalian studies, the database is organized by organ/system and animal species in Figure 8, by organ/system and exposure route in Figure 9, and by organ/system and exposure duration/lifestage in Figure 10.

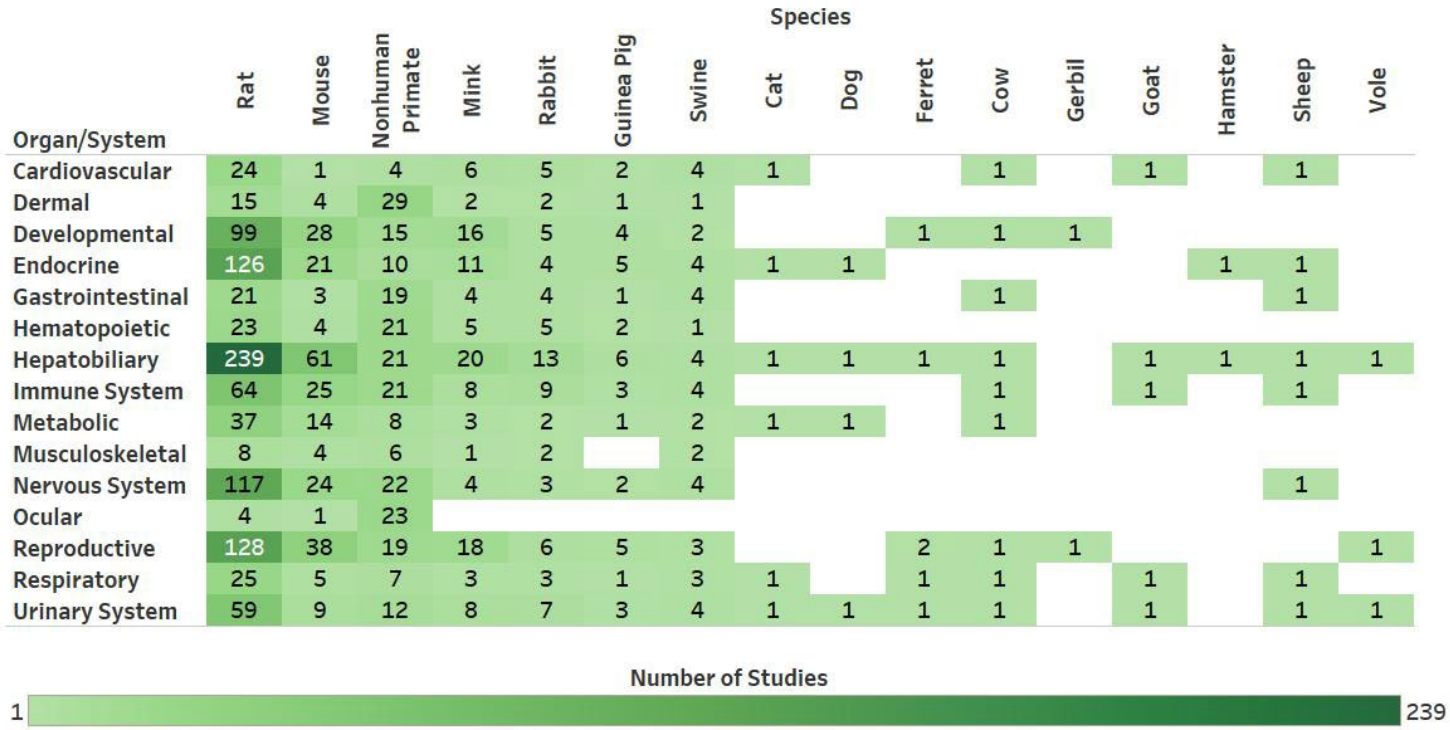


**Figure 8. Overview of Nonhuman Mammalian Studies by Organ/System and Species**

Summary of the database of studies in nonhuman mammals evaluating exposures to PCB mixtures and health endpoints organized by system and species. Lists of studies included in each count can be accessed via the online interactive version of this figure (https://hawc.epa.gov/summary/visual/assessment/100500282/OverviewNonhumanMammalStudies/). The online figure can be expanded to include information by endpoint category and can be filtered by organ/system (options: cardiovascular, dermal, developmental, endocrine, gastrointestinal, hematopoietic, hepatobiliary, immune system, metabolic, musculoskeletal, nervous system, ocular, reproductive, respiratory, urinary system), exposure duration/life stage (options: acute [single dose], chronic, developmental, NR, short-term, subchronic), species (options: cat, cow, dog, ferret, gerbil, goat, guinea pig, hamster, mink, mouse, nonhuman primate, rabbit, rat, sheep, swine, vole), sex (relevant only for reproductive endpoints; options: female, male, pair), and exposure route (options: dermal, inhalation, injection, oral). Shading intensity corresponds with the number of studies in each category, from 1 to 239, which is the maximum number of studies in any category. NR=not reported.

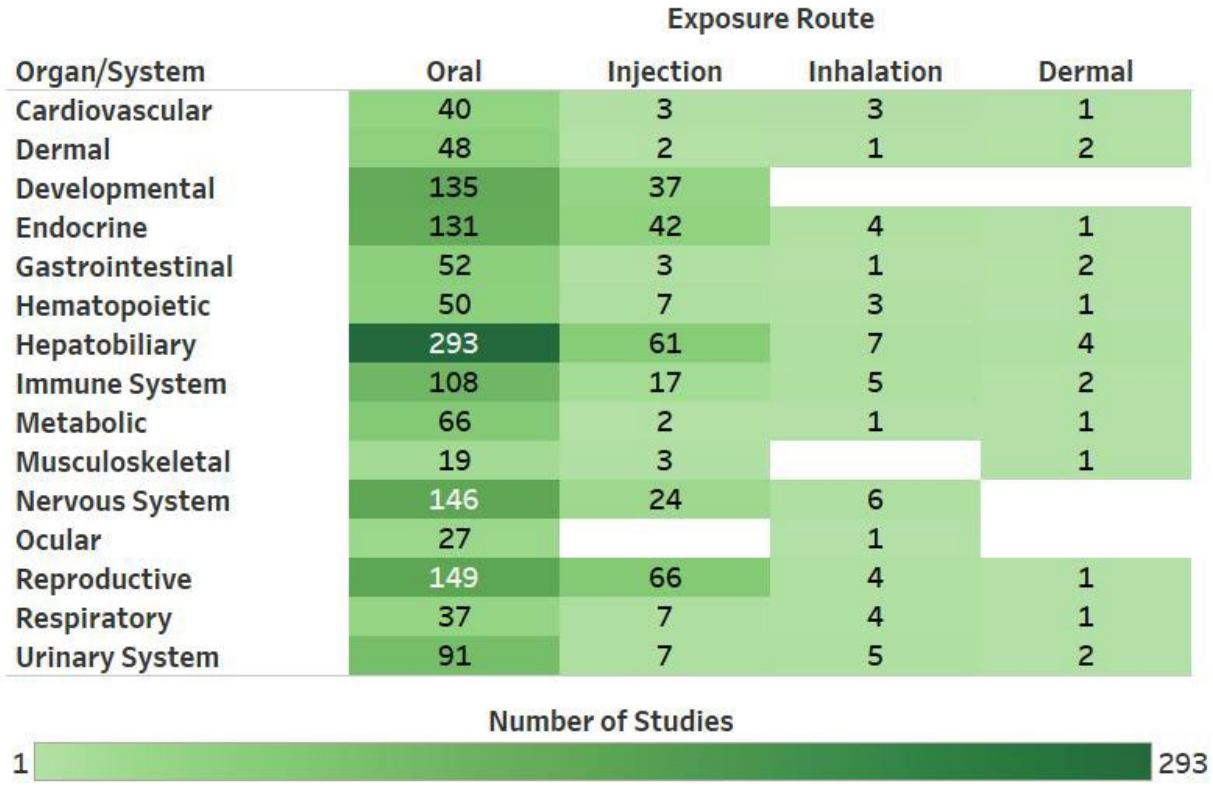


**Figure 9. Overview of Nonhuman Mammalian Studies by Organ/System and Exposure Route**

Summary of the database of studies in nonhuman mammals evaluating exposures to PCB mixtures and health endpoints organized by system and exposure route. "Oral" included gavage, diet, drinking water, and intragastric exposures, "injection" included intravenous, subcutaneous, and intraperitoneal exposures, "inhalation" included whole-body or nose-only inhalation exposures, and "dermal" included occlusive, semiocclusive, and nonocclusive dermal exposures. Lists of studies included in each count can be accessed via the online interactive version of this figure (https://hawc.epa.gov/summary/visual/assessment/100500282/OverviewNonhumanMammalStudies/). The online figure can be expanded to include information by endpoint category and can be filtered by organ/system (options: cardiovascular, dermal, developmental, endocrine, gastrointestinal, hematopoietic, hepatobiliary, immune system, metabolic, musculoskeletal, nervous system, ocular, reproductive, respiratory, urinary system), exposure duration/life stage (options: acute [single dose], chronic, developmental, NR, short-term, subchronic), species (options: cat, cow, dog, ferret, gerbil, goat, guinea pig, hamster, mink, mouse, nonhuman primate, rabbit, rat, sheep, swine, vole), sex (relevant only for reproductive endpoints; options: female, male, pair), and exposure route (options: dermal, inhalation, injection, oral). Shading intensity corresponds with the number of studies in each category, from 1 to 293, which is the maximum number of studies in any category. NR=not reported.

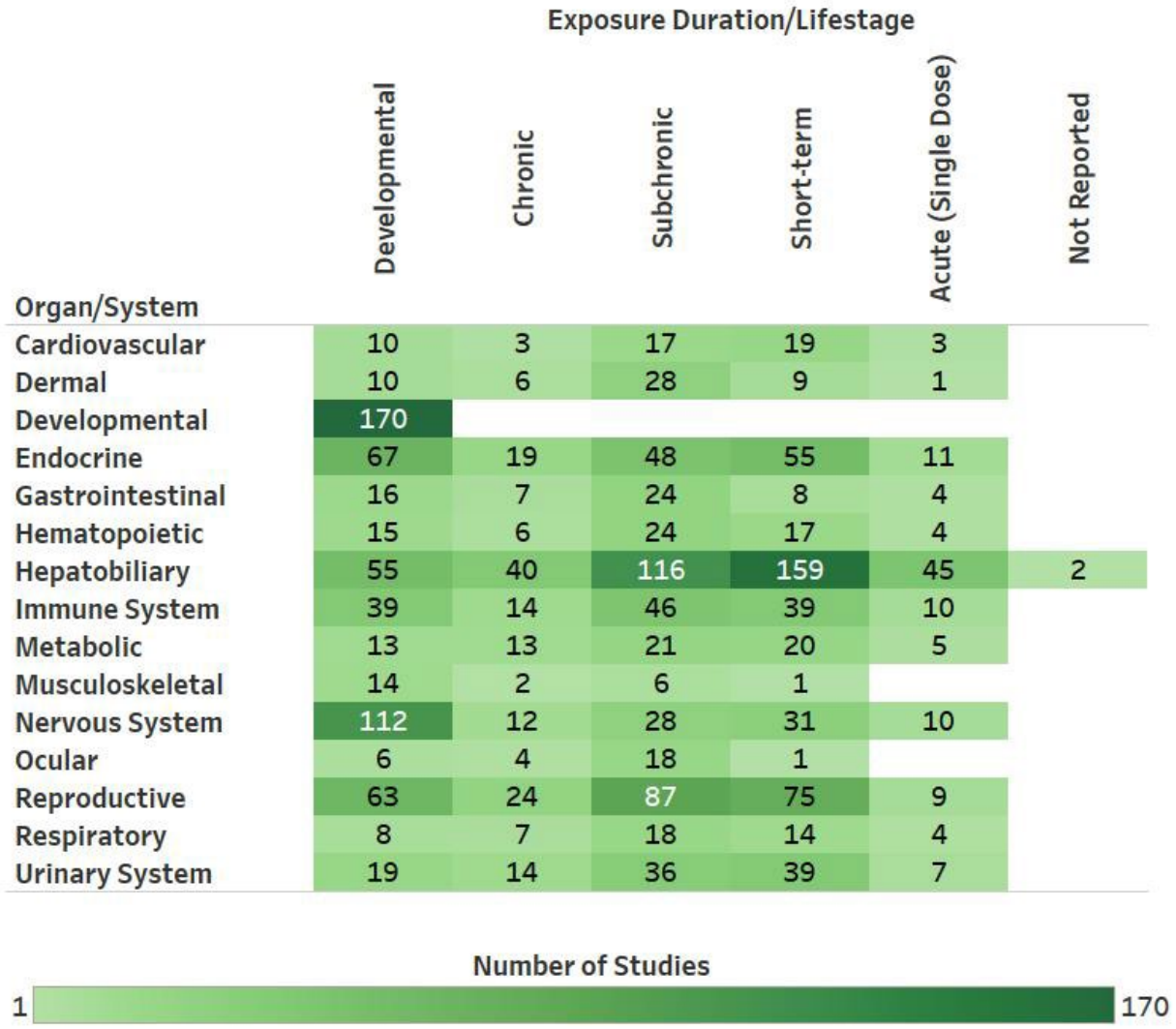


**Figure 10. Overview of Nonhuman Mammalian Studies by Organ/System and Exposure Duration/Lifestage**

Summary of the database of studies in nonhuman mammals evaluating exposures to PCB mixtures and health endpoints organized by system and exposure duration/lifestage. Lists of studies included in each count can be accessed via the online interactive version of this figure (https://hawc.epa.gov/summary/visual/assessment/100500282/OverviewNonhumanMammalStudies/). The online figure can be expanded to include information by endpoint category and can be filtered by organ/system (options: cardiovascular, dermal, developmental, endocrine, gastrointestinal, hematopoietic, hepatobiliary, immune system, metabolic, musculoskeletal, nervous system, ocular, reproductive, respiratory, urinary system), exposure duration/life stage (options: acute [single dose], chronic, developmental, NR, short-term, subchronic), species (options: cat, cow, dog, ferret, gerbil, goat, guinea pig, hamster, mink, mouse, nonhuman primate, rabbit, rat, sheep, swine, vole), sex (relevant only for reproductive endpoints; options: female, male, pair), and exposure route (options: dermal, inhalation, injection, oral). NR = not reported. Shading intensity corresponds with the number of studies in each category, from 1 to 170, which is the maximum number of studies in any category. NR=not reported.

### 3.3.1. Cardiovascular

The cardiovascular system is complex, consisting of the heart and a closed system of blood vessels: arteries, capillaries, and veins. The heart pumps oxygenated blood from the lungs to the aorta, from which the blood is further carried to peripheral arteries and then the capillaries in the organs and tissues of the body. Deoxygenated blood from organs and tissues is carried from the capillaries to the peripheral veins and further to the heart.

Eighty-one human studies evaluated cardiovascular endpoints and PCB exposure (see Figure 4). Studied endpoints included ischemic heart disease (IHD; also referred to as coronary artery disease or coronary heart disease); myocardial infarction (MI; heart attack); hypertension (high blood pressure); cerebrovascular disease; atherosclerosis (plaque buildup inside arteries and hardening and narrowing of their walls); and heart failure (HF; inability to pump sufficient blood to organs and tissues). These health endpoints are interrelated—IHD is caused by decreased blood flow through coronary arteries due to atherosclerosis resulting in myocardial ischemia. The two most severe, immediately life-threatening cardiovascular endpoints are MI and stroke, which are the most severe forms of IHD and cerebrovascular disease, respectively. Hypertension is a major risk factor for MI and stroke and for kidney failure, which is discussed in detail in Section 3.3.15. Dyslipidemias, considered important risk factors for cardiovascular disease, are discussed in detail in Section 3.3.7.

Among the cardiovascular endpoints evaluated in the literature, those comprising well-defined specific disorders of the cardiovascular system objectively confirmed by study investigators (hypertension confirmed by blood pressure measurement; atherosclerosis confirmed by intima-media thickness assessed by the ultrasound imaging) or by physicians (diagnoses of IHD, MI, hypertension, stroke in medical records) are expected to be the most sensitive and specific. As noted above, cardiovascular endpoints are pathogenetically interrelated; thus, if PCB exposure does affect the cardiovascular system, one might anticipate finding associations with multiple related endpoints. However, endpoints that are overly broadly defined (cardiovascular system diseases not otherwise specified [NOS] or heart disease NOS), self-reported endpoints, and subjective cardiovascular complaints are more likely to capture a range of disease severities and etiologies. For example, cardiovascular system diseases NOS comprise a very broad group of disorders ranging from IHD to infectious inflammation caused by various infectious pathogens (such as endocarditis and myocarditis) to valvular heart disease (e.g., as a result of rheumatic fever), and even to peripartum cardiomyopathy. Cardiovascular disorders caused by infectious pathogens or pregnancy differ fundamentally from atherosclerotic cardiovascular disease by their etiology and pathogenesis; thus, studies of cardiovascular system diseases NOS and other broadly defined endpoints are less useful for identifying potential cardiovascular effects due to PCB exposure.

Among the 81 human studies (see Figure 4), many investigated more than one relevant endpoint. Overall, 19 studies evaluated mortality due to cardiovascular disease, and 7 of these also evaluated mortality due to cerebrovascular disease (see Figure 11); other studies evaluated IHD

[n = 5, including 4 evaluating MI (Bergkvist et al., 2016; Raymond et al., 2016; Bergkvist et al., 2015; Van Larebeke et al., 2015)], hypertension [n = 39, including 4 evaluating blood pressure in prenatally exposed children (Güil-Oumrait et al., 2021; Warembourg et al., 2019; Lee et al., 2016; Vafeiadi et al., 2015)], cerebrovascular disease [n = 8, including 6 evaluating stroke (Li et al., 2020; Lim et al., 2018; Kippler et al., 2016; Raymond et al., 2016; Bergkvist et al., 2014; Lee et al., 2012)], development of atherosclerosis (n = 3), heart failure (n = 1), subjective cardiovascular complaints (n = 5), heart rate variability (Liberda et al., 2021), fetal heart rate following maternal exposure (DiPietro et al., 2014), "diseases of the heart" or cardiovascular system diseases not otherwise specified [NOS; n = 8, including 1 evaluating heart disease NOS (Ha et al., 2007)], and pharmaceutical consumption of cardiovascular disease medications (n = 1).

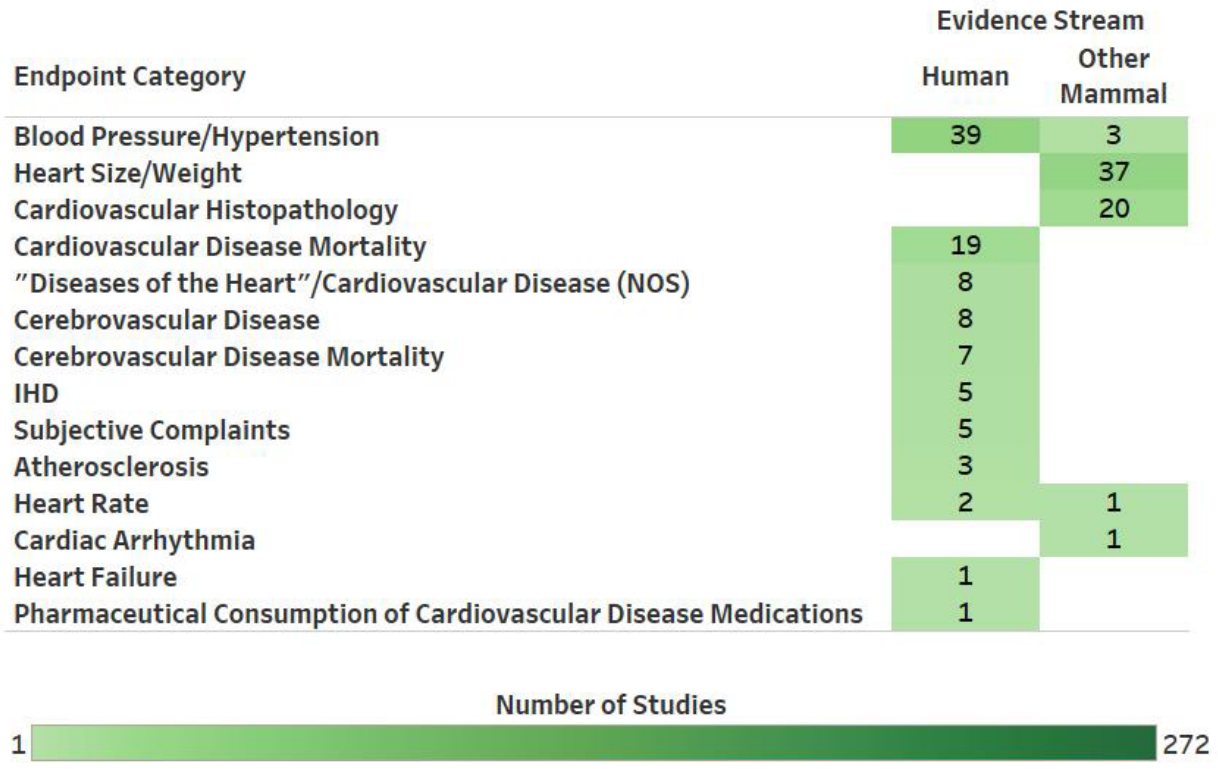


**Figure 11:Overview of Human and Other Mammalian Cardiovascular Studies**

Summary of the database of studies evaluating exposures to PCB mixtures and cardiovascular endpoints organized by endpoint category. Lists of studies included in each count can be accessed via the online interactive version of this figure (https://hawc.epa.gov/summary/visual/assessment/100500282/OverviewAllStudies/). Shading intensity corresponds with the number of studies in each category, from 1 to 272, which is the maximum number of nonhuman mammalian studies in any health endpoint category. The intent is to highlight not only differences in the distribution of studies across cardiovascular endpoint categories but also to emphasize the number of cardiovascular studies relative to the number of studies for other organs/systems. IHD = ischemic heart disease; NOS = not otherwise specified.

Forty-seven papers were identified in which experimental mammals were exposed to PCB mixtures and cardiovascular endpoints were evaluated (see Figure 4). Exposures to PCB mixtures have been studied in a variety of nonhuman mammalian models, including rats, mice, rhesus monkeys, mink, rabbits, guinea pigs, and swine (see Figure 8). These animals have been exposed to PCBs by oral, injection, inhalation, and dermal routes (see Figure 9). One important challenge in experimental studies of cardiovascular endpoints is the resistance of wild-type rodents (specifically, mice and rats) to the development of vascular toxicity (Zhao et al., 2020b; Oppi et al., 2019). Piglets and monkeys are much better models of cardiovascular toxicity (Daugherty et al., 2017); however, these species have been underutilized in toxicology studies. In contrast to humans, rodents do not develop spontaneous IHD, MI, HF, or stroke. Because of these differences, drawing inferences about human cardiovascular health risk based on the results of rodent studies can be especially challenging. The most common cardiovascular endpoint categories evaluated in studies of PCB-exposed mammals other than humans included heart size/weight, cardiovascular histopathology, and blood pressure (see Figure 11).

Of the 19 human studies that investigated the most extreme endpoint—death (mortality)—almost half evaluated reasonably specific and clinically meaningful endpoints of mortality from IHD along with death due to at least one other cardiovascular endpoint: cerebrovascular disease (Kimbrough et al., 2015; Ruder et al., 2014; Prince et al., 2006b; Prince et al., 2006a; Mallin et al., 2004; Kimbrough et al., 2003; Gustavsson and Hogstedt, 1997), hypertension (Kimbrough et al., 2015; Ruder et al., 2014; Prince et al., 2006b; Prince et al., 2006a; Mallin et al., 2004; Kimbrough et al., 2003), or cardiovascular disease NOS (Ruder et al., 2006; Gustavsson et al., 1986). Ten mortality studies evaluated death only from cardiovascular diseases/heart disease NOS, an overly broadly defined cause (Donat-Vargas et al., 2020a; Kim et al., 2015b; van Wijngaarden et al., 2001; Sinks et al., 1992a; Sinks et al., 1992b; Sinks et al., 1990; Fitzgerald et al., 1989; Bertazzi et al., 1987; Brown, 1987; Brown and Jones, 1981). As stated above, such studies lack specificity, which makes them less useful for identifying potential associations between PCB exposure and atherosclerotic cardiovascular disease. Two nonoccupational studies examined mortality from cardiovascular diseases NOS: one within the Swedish Infrastructure for Medical Population-based Life-course and Environmental Research cohort that included the Swedish Mammography Cohort and the Cohort of Swedish Men (Donat-Vargas et al., 2020a) and one in older adult participants within the National Health and Nutrition Examination Survey (NHANES) (Kim et al., 2015b). The remaining mortality studies were conducted in occupational cohorts (see Figure 5), and of these, most were conducted in (sometimes overlapping) groups of capacitor manufacturing workers.

Hypertension was the most commonly studied endpoint in humans (n = 39) (see Figure 11). This is in addition to six studies of mortality due to hypertension (Kimbrough et al., 2015; Ruder et al., 2014; Prince et al., 2006b; Prince et al., 2006a; Mallin et al., 2004; Kimbrough et al., 2003). The 39 nonmortality hypertension studies investigated the development or prevalence of hypertension using cohort, nested case-control, and cross-sectional study designs (see Figure 6). Among these

studies, only one was conducted in a capacitor manufacturing workers cohort; the remaining studies were conducted in samples of the general population (such as NHANES and a cohort of the graduates of the University of Navarra, Spain), in samples of populations exposed by fish or marine mammal consumption, in samples of populations residing in proximity to PCB manufacturing facilities, and Yusho and Yu-Cheng populations (see Figure 5). Of these nonoccupational studies, those conducted in samples of the general population might be most informative for evaluating potential effects of relatively lower levels of PCB exposure. Most of the nonoccupational nonmortality hypertension studies used objective measures of hypertension—either blood pressure (BP) measured by the investigators or diagnosis of hypertension from subjects' medical records; only seven used self-reported hypertension as the endpoint (Aminov and Carpenter, 2020; Zani et al., 2019; Raymond et al., 2016; Donat-Vargas et al., 2015; Van Larebeke et al., 2015; Goncharov et al., 2008; Stehr-Green et al., 1986). Many studies used multiple measurements of BP to mitigate information (measurement) bias known as "white coat hypertension" or "office hypertension." For example, a study of serum concentrations of persistent organic pollutants and prevalence of hypertension conducted by Ha et al. (2009) used the results from NHANES 1999–2002, in which BP of the participants was measured at least three times, and the average values of systolic and diastolic BP were used for analysis. The Ewha Birth and Growth cohort study evaluating persistent organic pollutant exposure and health endpoints in Korean children averaged two measurements of BP taken 5 minutes apart (Lee et al., 2016). PCB exposures and BP were examined in three nonhuman mammalian studies (see Figure 11), including a study of orally exposed mice (Wahlang et al., 2017), a study of rat offspring exposed during gestation and lactation (Dziennis et al., 2008), and an acute duration study using i.v. administration in cats (Righter et al., 1976).

Five studies evaluated nonfatal IHD (see Figure 11), all in nonoccupational settings. Two evaluated only MI (Bergkvist et al., 2016; Bergkvist et al., 2015), and three evaluated multiple endpoints: MI, hypertension and cerebrovascular disease (Van Larebeke et al., 2015); IHD and cerebrovascular disease (Pines et al., 1986); and IHD, MI, hypertension, and stroke (Raymond et al., 2016). Studies conducted by Bergkvist et al. (2015) using the Swedish Mammography Cohort and by Bergkvist et al. (2016) using the Cohort of Swedish Men presented findings for MI ascertained from validated national registry data. In contrast, studies conducted by Van Larebeke et al. (2015) using the Flemish Environment and Health Survey and a study of male anglers in Wisconsin by Raymond et al. (2016) only provided information on self-reported endpoints of MI (Raymond et al., 2016; Van Larebeke et al., 2015) and IHD (Raymond et al., 2016). Self-report might be a less reliable measure, although this is less of a concern for significant, severe events such as MI, which are likely to be recalled with greater accuracy.

Cerebrovascular disease was investigated in 15 studies, including 7 mortality studies (all in occupational settings) (see Figure 11), 2 nonfatal cerebrovascular disease studies in a general population setting (Van Larebeke et al., 2015; Pines et al., 1986), and 6 nonfatal stroke studies in

nonoccupational settings (Li et al., 2020; Lim et al., 2018; Kippler et al., 2016; Raymond et al., 2016; Bergkvist et al., 2014; Lee et al., 2012). Stroke is a better-defined endpoint than a broader diagnostic category for cerebrovascular disease that includes not only stroke, but some other disorders, for example, a rare congenital cerebral aneurism, not likely to be causally associated with PCB exposure. Among the six studies of nonfatal stroke, five included objectively verified diagnosis of stroke: three studies used only hospital-treated strokes (Li et al., 2020; Lim et al., 2018; Lee et al., 2012), and two used validated Swedish Patient Register and the Swedish Cause of Death Register (Kippler et al., 2016; Bergkvist et al., 2014). One study conducted among male anglers in Wisconsin used a less reliable measure of stroke self-report (Raymond et al., 2016), although recall bias is not of significant concern given the severity of stroke as a life event.

Atherosclerosis has been evaluated in only three studies of PCB exposure (see Figure 11). However, these studies did include an evaluation of sensitive and specific markers of atherosclerosis, such as carotid plaques and intima-media thickness (Liberda et al., 2019; Lind et al., 2012) and coronary artery calcium score (Donat-Vargas et al., 2020b). No studies of atherosclerosis in laboratory mammals exposed to PCB mixtures were identified; however, atherosclerosis and associated mechanistic endpoints (e.g., aortic expression of vascular cell adhesion molecule-1) have been evaluated following intraperitoneal exposure to individual PCB congeners in genetically altered mice that model human cardiovascular disease (Petriello et al., 2018; Murphy et al., 2015; Hennig et al., 2002).

Other cardiovascular endpoints investigated infrequently in human studies included left ventricular systolic and diastolic dysfunction (i.e., heart failure) (Sjöberg Lind et al., 2013), heart rate variability (Liberda et al., 2021), and fetal heart rate following maternal PCB exposure (DiPietro et al., 2014). Two nonhuman mammalian studies of endpoints related to cardiac function are available to supplement the information gathered in human studies (Willett et al., 1987; Righter et al., 1976).

Finally, five human studies evaluated subjective complaints of chest pain (Broding et al., 2008; Emmett et al., 1988b), general cardiovascular complaints (Peper et al., 2005), subjective complaints and broad clinical measures (heart rate, blood pressure, and heart sounds) (Kanagawa et al., 2008), and the Subjective Complaint List for Children and Adolescents (Liebl et al., 2004) as cardiovascular endpoints. However, such complaints are less useful for evaluating potential health effects of PCB exposure due to their nonspecific and self-reported nature.

In addition to the endpoints described above, studies of nonhuman mammals exposed to PCB mixtures also evaluated endpoints such as cardiovascular histopathology and heart size/weight in diverse species, including rhesus monkeys, rats, guinea pigs, rabbits, mink, and swine (see Figure 8). As mentioned above, rodent models are relatively insensitive to the development of vascular toxicity (Zhao et al., 2020b), so it is notable that this database does include some studies of PCB-exposed pigs and monkeys (see Figure 8). Some studies of nonhuman mammals exposed to PCB mixtures included evaluations following exposure during prenatal and

postnatal developmental periods (see Figure 10). Heart weight was the cardiovascular endpoint studied most often in mammals other than humans (see Figure 11). Evaluations of heart weight and PCB exposure can be further supported by the inclusion of other types of data (e.g., heart histopathology or endpoints related to cardiac function). Of the 37 nonhuman mammalian studies that evaluated heart size/weight and PCB exposure, 12 also included assessments of other cardiovascular endpoints, most often histopathological evaluations (Chu et al., 2008; Blake et al., 2000; Hornshaw et al., 1986; Price et al., 1979; Allen et al., 1976; Hansen et al., 1975; Itokawa et al., 1975; Linder et al., 1974; Bruckner et al., 1973; Koller and Zinkl, 1973; Vos and de Roij, 1972; Vos and Beems, 1971).

In summary, the human database, supplemented with data from nonhuman mammalian studies conducted using sensitive and informative models and methods, is likely to provide enough information to evaluate the potential for PCB-associated effects on the cardiovascular system. However, further study of PCB exposures and atherosclerosis and other cardiovascular endpoints in humans and in genetically altered mouse models of human vascular diseases is warranted to fully address the potential for PCB cardiovascular toxicity.

### 3.3.2. Dermal

Dermal endpoints relate to the outer layer of the body, including skin and subcutaneous tissue, some mucous membranes (e.g., gingivae), and fingernails and toenails. The main function of these tissues is to act as a protective barrier, and they are among the first tissues to contact exogenous agents. Responses of the skin and nails to chemical exposures can include dermal irritation and scar formation; and, specifically in the case of exposures to halogenated aromatic hydrocarbons, especially dioxin-like chemicals, acne and chloracne (Ju et al., 2009). Other endpoints evaluated with PCB exposure include abnormal pigmentation, deformities in fingernails or toenails, hyperkeratosis, and gingival swelling or recession. Studies in mammals other than humans also evaluated alopecia, dermal/subcutaneous histopathology, and wound healing. Although some of these endpoints could be perceived as less severe than those evaluated for other organs/systems, effects on dermal endpoints can negatively impact quality of life, potentially resulting in physical discomfort and anxiety and depression (Barankin and Dekoven, 2002).

In the database of PCB exposure studies, 34 human studies and 52 studies in other mammals evaluated dermal endpoints (see Figure 4). Of the human studies, most were reports of occupational exposures, Yu-Cheng or Yusho poisoning, or other accidental exposures (see Figure 5). In many of these studies, the dermal endpoints were symptoms reported or clinical observations after the exposure. Many dermal endpoints reported were part of the initial diagnosis and were not necessarily the focus of the publications. Other human studies included two conducted among general population samples (Smit et al., 2015; Lee et al., 2008), one cross-sectional study in a population living in a highly polluted area (Arisi et al., 2021), and one cross-sectional study of people living near waste sites (Stehr-Green et al., 1986). This study only evaluated self-reported, physician-diagnosed skin problems without further description.

The most studied endpoint category was acne/chloracne in both humans and other mammals (see Figure 12). Eight studies in humans evaluated subjects from the Yusho and Yu-Cheng cohorts, and 12 were conducted among populations with other accidental or occupational exposures (see Figure 5). The remaining studies were conducted in populations with exposure via diet (Dewailly et al., 2000) or living in a highly polluted area (Arisi et al., 2021). Although these studies, especially those conducted in the Yusho and Yu-Cheng cohorts, might have additional exposures to dioxin-like chemicals other than PCBs that could contribute to acne/chloracne, several studies in other mammals might help determine whether PCB exposure alone is sufficient to cause this dermal effect. Other dermal endpoints evaluated in other mammals and in human populations with relatively high exposure levels, such as occupational and the Yusho and Yu-Cheng cohorts, include abnormal pigmentation (18 human and 8 studies in other mammals), dermal irritation (18 human and 6 studies in other mammals), hyperkeratosis (6 human and 12 studies in other mammals), and fingernail and toenail deformities (8 human and 13 studies in other mammals) (see Figure 12). Although many studies in nonhuman mammals evaluated alopecia or subcutaneous edema, these endpoints were not described in human studies. In addition, 19 studies in other mammals evaluated dermal histopathology. Nonhuman mammalian studies of dermal histopathology could complement the data from human studies. Less commonly studied endpoints included gingival swelling or recession (one human and four studies in other mammals), scar formation (one human study), and wound healing (one study in mice).

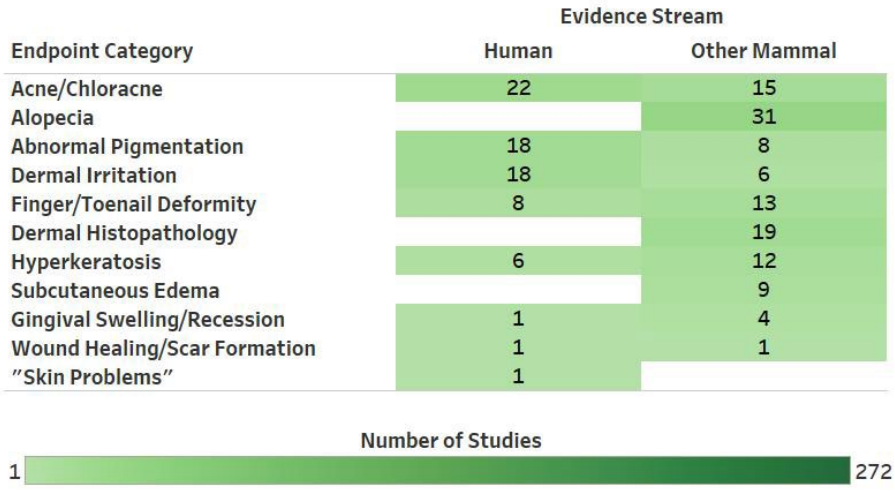


**Figure 12:Overview of Human and Other Mammalian Dermal Studies**

Summary of the database of studies evaluating exposures to PCB mixtures and dermal endpoints organized by endpoint category. Lists of studies included in each count can be accessed via the online interactive version of this figure (https://hawc.epa.gov/summary/visual/assessment/100500282/OverviewAllStudies/). Shading intensity corresponds with the number of studies in each category, from 1 to 272, which is the maximum number of nonhuman mammalian studies in any health endpoint category. The intent is to highlight not only differences in the distribution of studies across dermal endpoint categories but also to emphasize the number of dermal studies relative to the number of studies for other organs/systems.

Although most human studies available for dermal endpoints were focused on populations with potential for relatively high exposure, two studies were conducted among general population samples, including one prospective birth cohort (Smit et al., 2015) and a population-based cross-sectional survey (NHANES) focused on periodontal disease (Lee et al., 2008). The study conducted in a birth cohort was focused on immune endpoints but included evaluations of eczema, a form of dermal irritation often associated with atopic immune reactions. As such, studies of eczema are also considered in Section 3.3.8.

Most of the 52 nonhuman mammalian studies (see Figure 4) were conducted in nonhuman primates, followed by rats, mice, and other species, with 2 studies using more than one species (Kunita et al., 1984; Thomas and Hinsdill, 1978) (see Figure 8). Of the mammalian species evaluated, nonhuman primates are most similar to humans and could provide the strongest animal evidence linking PCBs to dermal endpoints in humans. All but five nonhuman mammalian studies evaluated endpoints following only oral PCB administration (see Figure 9). The remaining studies included a subchronic inhalation study in rats (Casey et al., 1999), a 10-day injection study in mice (Watanabe and Sugahara, 1981), an acute injection study in mice (Pillai et al., 2020), and two subchronic dermal exposure studies in rabbits (Vos and Notenboom-Ram, 1972; Vos and Beems, 1971).

Overall, the bulk of the human database is limited to events of high PCB exposure including accidental and occupational exposures that generally provide qualitative information on dermal symptoms and are likely to include exposures to other compounds that could cause the same types of effects. Few studies of dermal endpoints in humans exposed at PCB levels experienced in the general population are available. Dermal endpoints in these studies are limited to periodontal disease and eczema. However, the combined human and animal database is likely to provide enough information to draw conclusions about the potential for PCB exposure to cause dermal effects, especially at relatively high exposure levels.

### 3.3.3. Developmental

Fetal development and early childhood can be particularly sensitive stages for adverse effects from exposure to environmental agents, as they are periods of rapid growth and development that can be affected by a range of toxicants through diverse biological mechanisms. Although exposures during development can impact any biological system, for the purpose of this review, developmental endpoints included in this domain are as follows: offspring mortality; body weight and size in early life, which includes fetal growth, anthropometric measures at birth, and childhood height or weight status and rates of growth; birth defects; placental weight/histopathology; and, in mammals, timing of postnatal developmental milestones, such as eye opening and pinna detachment. Exposures that occur at critical developmental stages for specific target organ systems (e.g., nervous, reproductive, and endocrine systems) could also result in negative health impacts in neonatal or adult life. These other potential effects of developmental

exposures, including those that could occur from parental exposure and influence reproductive capacity, are described in the sections devoted to those organs/systems.

Developmental effects resulting from exposure are critical to consider due to their substantial health and economic costs, which persist across the lifespan. For example, low birth weight and fetal growth restriction are associated with increased risk of infant mortality and morbidity and increased risk for disorders later in life such as metabolic disorders, type II diabetes, obesity, elevated blood pressure, and cardiovascular disease (Nobili et al., 2008; Barker, 2006; Gluckman and Hanson, 2006). The small decrements in size at birth for gestational age (even if size is classified in the normal range) caused by an inadequate fetal environment, could have health consequences later in life (Gluckman and Hanson, 2006). Other measures of fetal growth (e.g., ultrasound scans) and specific anthropometric parameters (e.g., head circumference) have also been significantly associated with infant growth and neurodevelopment (Henrichs et al., 2010; van Batenburg-Eddes et al., 2010). Outcomes at the low end of the distributions (i.e., low birth weight, intrauterine growth restriction, small for gestational age) have been well characterized with regard to associated costs at the time they occur and throughout life. Extremes at the high end of these distributions (e.g., large for gestational age) might also be harmful and indicative of abnormal fetal development but are less studied in relation to chemical exposures.

Of the 130 human and 170 other mammalian studies identified on PCB exposure and developmental endpoints (see Figure 4), most focused on measures of birth weight or other aspects of fetal growth (see Figure 13). Most human studies of PCB exposure and birth weight used biomarkers of exposure, measuring various PCB congeners in maternal or cord blood (see Figure 7). Twenty-five studies used measures of PCB congeners in breast milk to estimate gestational exposures. Given the long half-life of certain PCB congeners in blood and the proximity of available biomarker measurements to the exposure window of interest, the data available to assess relationships between PCB exposure and birth weight are quite robust. For example, one report by Govarts et al. (2012) presented a meta-analysis of PCBs and birth weight among 12 European birth cohorts involving 7,990 participants who had PCB 153 concentrations measured in maternal blood, cord blood, or breast milk samples. Several cohort studies that explored PCB exposure and birth size continued follow-up of children, which enabled them to also investigate in utero exposure to PCBs and height/weight status and rates of growth at different ages or developmental stages in childhood [e.g., (Karlsen et al., 2017; Hertz-Picciotto et al., 2005)]. Less commonly, studies investigated PCB exposure and growth among children newly recruited at various ages [e.g., (Burns et al., 2020)]. However, differences are notable in the timing and nature of the growth measurements and in the exposure period assessed (e.g., PCBs measured in samples collected in pregnancy/at delivery versus samples collected in childhood). Placental weight or placental histology was measured in several human and nonhuman mammalian studies (see Figure 13). Although placental weight is positively associated with fetal growth and birth weight, the human health relevance of this measure in isolation remains uncertain; however, placental dysfunction can

be detrimental to fetal viability. PCB exposure and body weight and size in early life were also evaluated in 148 studies of a wide variety of nonhuman mammalian species (see Figure 13), including nonhuman primates and various strains of mice and rats (see Figure 8); these studies could be useful to support the findings in human studies.

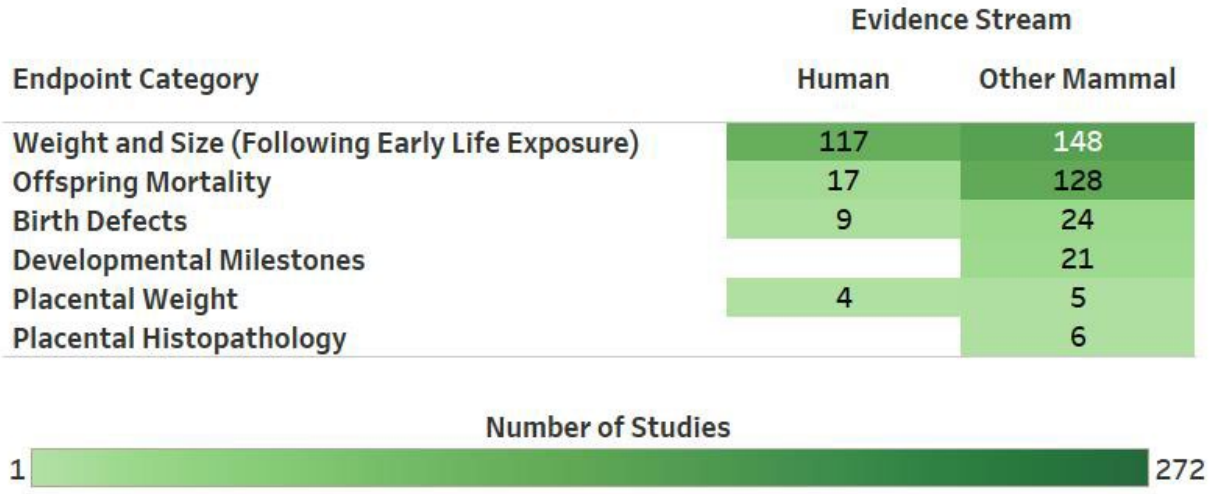


**Figure 13: Overview of Human and Other Mammalian Developmental Studies**

Summary of the database of studies evaluating exposures to PCB mixtures and developmental endpoints organized by endpoint category. Lists of studies included in each count can be accessed via the online interactive version of this figure (https://hawc.epa.gov/summary/visual/assessment/100500282/OverviewAllStudies/). Shading intensity corresponds with the number of studies in each category, from 1 to 272, which is the maximum number of nonhuman mammalian studies in any health endpoint category. The intent is to highlight not only differences in the distribution of studies across developmental endpoint categories but also to emphasize the number of developmental studies relative to the number of studies for other organs/systems.

Seventeen human studies investigated PCB exposure and miscarriage, stillbirth, or infant mortality (see Figure 13). These studies varied in design and sample size; results for stillbirth typically involved few cases, and differences in study design (e.g., timing of recruitment, method of outcome ascertainment, and ability to adequately detect early pregnancy losses) can limit the ability to synthesize results for miscarriage across studies. However, these data can be supplemented by information from 128 studies in other mammals that assessed offspring viability in the context of PCB exposure, many including direct measures such as observation of stillborn pups and others relying on indirect measures such as litter size.

Birth defects (e.g., neural tube defects) and PCB exposure were investigated in nine human studies (see Figure 13). Birth defects and other endpoints associated with testicular dysgenesis syndrome (Skakkebaek et al., 2001), including cryptorchidism and hypospadias, are included in Section 3.3.13. In general, the human studies of birth defects are few and tend to have few cases, which limits the robustness of the overall findings. Twenty-four studies of PCB exposure and birth

defects in other mammals, including skeletal malformation and cleft palate, can provide additional information on potential causal relationships. Twenty-one studies in nonhuman mammals investigated PCB exposure and the timing of postnatal developmental milestones, such as eye opening and pinna detachment. Changes in the timing of these milestones could be informative together with other measures of growth and development, but the human health relevance of these endpoints observed in isolation is uncertain.

Overall, the strength of the database for assessing human evidence of relationships between PCB exposure and developmental endpoints is high for birth weight, including both continuous measures of birth weight and, from many studies, dichotomized outcomes based on size at birth (low birth weight, small for gestational age) and other measures that can be collected at birth, such as birth length and head circumference. The strength of the human evidence for other developmental endpoints is limited by few studies, small sample sizes or numbers of cases, and important variations in study designs across cohorts. However, nonhuman mammalian studies of similar endpoints are often available and represent exposures in multiple species at a wide range of doses, routes, durations, and developmental timings; these could provide additional information useful for evaluating potential hazards of PCB exposure.

### 3.3.4. Endocrine

Endocrine organs synthesize and secrete hormones, chemical messengers that travel through the blood stream to bind to specific receptors and initiate biological responses at target tissues. Major endocrine organs include the hypothalamus, pituitary, testes, ovaries, pancreas, thyroid, and the adrenals. The focus here is on thyroid and adrenal endpoints because of the potential for the PCB literature to support exposure-response evaluations for these endpoints, which regulate physiological processes related to metabolism, growth and development, stress response, and immunity. Studies of PCBs and sex-steroid hormones are discussed in Section 3.3.13, and studies of insulin are discussed in Section 3.3.9. Thyroid and adrenal activity are regulated by hypothalamic and pituitary hormones through negative feedback pathways, comprising the hypothalamus-pituitary-thyroid (HPT) and hypothalamus-pituitary-adrenal (HPA) axes. Peripheral tissue deiodinases catalyze conversion of thyroxine (T4), a thyroid prohormone, to biologically active triiodothyronine (T3). A system of hepatic serum carrier proteins governs hormone bioavailability. Endocrine responses to chemical exposures could include thyroid disease, differences in circulating thyroid hormone concentrations, such as thyroid stimulating hormone (TSH), T4, and T3, and histopathological thyroid changes. Endocrine responses can also include differences in circulating adrenal hormone concentrations (e.g., adrenocorticotropic hormone [ACTH]), the glucocorticoids cortisol, cortisone, and their metabolites, and histopathological adrenal changes. Adrenal hormones also include sex-steroid and mineralocorticoid hormones.

Studies evaluating thyroid endpoints included 116 human studies and 113 studies in other mammals (see Figure 14); 15 human studies and 84 studies in other mammals evaluated adrenal endpoints. Few human or nonhuman mammalian studies evaluated other endocrine endpoints,

such as parathyroid endpoints, or levels of vitamin D, insulin-like growth factor, growth hormone, or melatonin. The lack of information for these other hormones precludes the ability to draw hazard conclusions.

| Endocrine Endpoint Category | | Evidence Stream: Human | Evidence Stream: Other Mammal |
|---|---|---|---|
| Thyroid Endpoints | | 116 | 113 |
| Adrenal Endpoints | | 15 | 84 |
| Pituitary Endpoints | | | 13 |
| Parathyroid Endpoints | | 1 | 6 |
| Insulin-Like Growth Factor | | 2 | 1 |
| Vitamin D | | 1 | 2 |
| "Endocrine Disease" | | 2 | |
| Growth Hormone | | 1 | |
| Melatonin | | | 1 |
| Thyroid Endpoints | HPT Hormones | 109 | 88 |
| | Thyroid Histopathology | | 41 |
| | Thyroid Size/Weight | 11 | 27 |
| | Thyroid Disease | 15 | |
| | Thyroid Nodules | 3 | |
| Adrenal Endpoints | Adrenal Weight | | 55 |
| | HPA Hormones | 15 | 33 |
| | Adrenal Histopathology | | 27 |
| Pituitary Endpoints | Pituitary Weight | | 9 |
| | Pituitary Histopathology | | 6 |
| Parathyroid Endpoints | Parathyroid Histopathology | | 4 |
| | Parathyroid Hormone | | 2 |
| | Parathyroid disease | 1 | |
| Insulin-Like Growth Factor | | 2 | 1 |
| Vitamin D | | 1 | 2 |
| "Endocrine Disease" | | 2 | |
| Growth Hormone | | 1 | |
| Melatonin | | | 1 |

Number of Studies

1 — 272

**Figure 14. Overview of Human and Other Mammalian Endocrine Studies**

Summary of the database of studies evaluating exposures to PCB mixtures and endocrine endpoints organized by endpoint category. Lists of studies included in each count can be accessed via the online interactive versions of this figure: (https://hawc.epa.gov/summary/visual/assessment/100500282/EndocrineEndpointsHumans/) for human studies; and (https://hawc.epa.gov/summary/visual/assessment/100500282/EndocrineEndpointsNonhumanMammals/) for studies of nonhuman mammals. These interactive summaries can be adjusted to group endocrine endpoint categories into three levels of organization. The interactive summary of the human database can be filtered by study design (options: case-control, cohort, cross-sectional, other), population (options: fish/marine mammal [diet], general population, occupational, residents in contaminated area, Yusho/Yu-Cheng), and exposure metric (options: adipose tissue, blood, breast milk, child blood, cord blood, maternal blood, occupational/JEM, other tissue). The interactive summary of the nonhuman mammalian database can be filtered by species (options: cat, dog, guinea pig, hamster, mink, mouse, nonhuman primate, rabbit, rat, sheep, swine), exposure duration/life stage (options: acute [single dose], chronic, developmental, short-term, subchronic), and exposure route (options: dermal, inhalation, injection, oral). Shading intensity corresponds with the number of studies in each category, from 1 to 272, which is the maximum number of nonhuman mammalian studies in any health endpoint category. The intent is to highlight not only differences in the distribution of studies across endocrine endpoint categories but also to emphasize the number of endocrine studies relative to the number of studies for other organs/systems. HPT = hypothalamus-pituitary-thyroid; HPA = hypothalamus-pituitary-adrenal.

The most informative endpoints for assessing the potential for PCBs to cause thyroid effects are clinical disease diagnoses, based on deviations in the amount of circulating TSH and unbound, or "free," T4 (FT4) concentrations compared to population-specific laboratory reference intervals (Chaker et al., 2017; De Leo et al., 2016). Fifteen human studies evaluated thyroid disease (see Figure 14); yet only six were based on a clinically confirmed diagnosis (Dufour et al., 2020; Han et al., 2019; Dufour et al., 2018; Petrosino et al., 2018; Raffetti et al., 2018; Nagayama et al., 2007a), raising the potential for outcome misclassification (Section 3.2.1). Except for a few case-control or cohort designs, the studies of thyroid disease were mostly cross-sectional (see Figure 14), which means that temporality of exposure preceding outcome is not ensured (Section 3.2.1). Even in the absence of a clinical thyroid disease diagnosis, altered thyroid hormone levels are also informative endpoints that can provide insight into subclinical changes in thyroid function, although distinguishing changes that are adaptive from those that are pathological is difficult at the individual level. Still, small shifts in hormones at the individual level might result in significant numbers of clinical disease cases at the population level. Numerous studies collected thyroid hormone measures in the absence of known clinical thyroid disease, including TSH on its own [e.g., (de Cock et al., 2017; Han et al., 2011; Lopez-Espinosa et al., 2010; Álvarez-Pedrerol et al., 2008a; Chevrier et al., 2007; Langer et al., 2006; Langer et al., 2003; Ribas-Fitó et al., 2003; Gerhard et al., 1998; Dewailly et al., 1993)] and in combination with FT4 [e.g.,(Abdelouahab et al., 2013; Dallaire et al., 2009a; Álvarez-Pedrerol et al., 2008b; Langer et al., 2007a; Maervoet et al., 2007; Takser et al., 2005; Sala et al., 2001; Longnecker et al., 2000)].The addition of total (i.e., including protein bound) and other iodothyronines (e.g., reverse T4) offers greater insight into the state of the HPT axis, and these hormones frequently accompanied TSH measures [e.g., (Benson et al., 2018; Roze et al., 2009)].Characteristics of well-conducted studies for evaluating changes in TSH and FT4 include measurement of these hormones repeatedly in a population with known iodine status, respectively using a highly sensitive third-generation assay and direct separation techniques coupled to mass spectrometry (e.g., equilibrium dialysis), which avoids potential biases from binding protein differences (Chaker et al., 2017; De Leo et al., 2016; Demers and Spencer, 2003). Although no studies in the database had all these design characteristics, two studies employed a direct FT4 separation technique (Chevrier et al., 2008; Steuerwald et al., 2000), one of which was a prospective investigation of PCB exposure in Faroese mothers and thyroid function among their newborns (Steuerwald et al., 2000), and another study measured children's thyroid hormones at both 6 and 12 months of age (Krönke et al., 2022). Most studies used appropriate tissue samples, although newborn cord blood hormones are impacted by parturition (Gupta et al., 2014) and reflect maternal hormone in part, possibly leading to misclassification in 11 studies (Kim et al., 2015a; Brucker-Davis et al., 2011; Dallaire et al., 2009b; Roze et al., 2009; Dallaire et al., 2008; Herbstman et al., 2008; Maervoet et al., 2007; Takser et al., 2005; Wang et al., 2005; Longnecker et al., 2000; Koopman-Esseboom et al., 1994), and similarly for thyroid hormones measured in newborn blood spots collected within 48 hours of delivery by 3 studies (Berlin et al., 2021; Kim et al., 2015a;

Herbstman et al., 2008). One study quantified thyroid hormones in breast milk collected 2–9 days postpartum (Matovu et al., 2021), although the relation to infant thyroid hormones was likely modest (Mallya and Ogilvy-Stuart, 2018). Plasma and serum levels of HPT hormones, including T3, FT3, T4, FT4, and TSH, were measured in 88 nonhuman mammalian studies (see Figure 14).

Subclinical structural thyroid gland changes evaluated in 11 human studies (Gaum et al., 2016; Trnovec et al., 2013; Langer et al., 2009; Trnovec et al., 2008; Langer et al., 2007a; Langer et al., 2007b; Langer et al., 2006; Langer et al., 2005; Langer et al., 2003; Langer et al., 2001; Murai et al., 1987), including differences in volume, echogenicity, and presence of nodules, could also inform thyroid effects, although they are less informative given potential intra- and interobserver variabilities. Many more studies investigated thyroid weight or histopathology in mammals other than humans (see Figure 14). Evaluations of thyroid structure in animals might provide supporting information for endpoints measured in humans, especially thyroid hormone levels. The 113 nonhuman mammalian studies investigating thyroid-related endpoints included analyses of rats, nonhuman primates (cynomolgus or rhesus monkeys), mice, mink, and other species (see Figure 8). Importantly, many studies measured thyroid weight or histopathology in conjunction with measurements of thyroid hormones [e.g., (Bowers et al., 2004; Kato et al., 2003; Hallgren and Darnerud, 2002; Hood et al., 1999; Liu et al., 1995; Seo and Meserve, 1995; Murk et al., 1991; Byrne et al., 1987; Collins and Capen, 1980b, a)].

Cortisol (a glucocorticoid adrenal hormone) is a preferred stress response biomarker for human studies (Lee et al., 2015) and the most informative endpoint to assess the potential for PCBs to cause adrenal effects. Multiple blood, urine, or saliva collections over time are recommended to accommodate diurnal variability and acute responses. Hair cortisol has also been used, as an integrated measure over time. However, of 15 human studies that measured adrenal hormones (see Figure 14), only 6 measured cortisol or its metabolites (Gaum et al., 2020; Miyashita et al., 2018; Xu et al., 2014; Persky et al., 2012; Persky et al., 2011; Romeo et al., 2009), all using a single biospecimen, and 1 study additionally measured adrenocorticotropic pituitary hormone (ACTH) (Xu et al., 2014). Seven studies measured dehydroepiandrosterone sulfate (DHEAS), another adrenal-specific biomarker (Gaum et al., 2020; Emeville et al., 2013; Persky et al., 2012; Rennert et al., 2012; Persky et al., 2011; Persky et al., 2001; Gerhard et al., 1998); as an androgenic biomarker, DHEAS is also discussed in Section 3.3.13. Other studies measured nonspecific hormone metabolites that are not as useful in assessing the potential for adrenal effects; for example, pregnanes [e.g., (D'Errico et al., 2016)] are metabolites common to both adrenal glucocorticoids and to adrenal and ovarian progestogens. Many studies were cross-sectional, but one was a longitudinal investigation (Gaum et al., 2020). Three others were prospective studies of gestational PCB exposure and offspring's HPA hormones (Miyashita et al., 2018; Su et al., 2015; Rennert et al., 2012). One measured cortisol (Miyashita et al., 2018), but one measured DHEAS only (Rennert et al., 2012), and one measured aldosterone only, an osmoregulatory hormone (Su et al., 2015). Of 84 nonhuman mammalian studies of HPA endpoints (see Figure 14), 45 were conducted in rats,

although studies were also identified examining rhesus monkeys, mice, mink, and other species (see Figure 8). Most nonhuman mammalian studies evaluated exposure to PCBs and adrenal weights or histopathology (see Figure 14). An additional 13 studies examined pituitary weight or histopathology (see Figure 14), and 1 nonhuman mammalian study measured corticotropin releasing hormone (CRH) and ACTH levels (Meserve et al., 1992). Serum or urinary glucocorticoid measurements were well represented in the nonhuman mammalian literature (see Figure 14). Critically, many studies measured adrenal hormones in conjunction with measurements of adrenal weight or histopathology [e.g., (Krishnan et al., 2019; Reilly et al., 2015; Meserve et al., 1992; Nagaoka et al., 1986; Dunn et al., 1983; Sanders et al., 1977; Sanders and Kirkpatrick, 1977; Zepp and Kirkpatrick, 1976; Sanders and Kirkpatrick, 1975; Bruckner et al., 1974)]. Whereas the literature database in humans is modest, observations in other mammals might provide important supporting information for evaluating glucocorticoid levels in humans exposed to PCBs.

In summary, a strong database of human studies for thyroid function is available, comprising multiple moderate to large prospective studies assessing occupational and nonoccupational PCB exposures, using valid endocrine biomarkers. The human database also includes a number of cross-sectional studies evaluating thyroid disease and function, although there is some uncertainty due to inability to establish temporality from cross-sectional evaluations (see Section 3.2.1). There is also an extensive database of nonhuman mammalian studies to inform the potential for PCBs to affect thyroid endpoints. The strength of the human database for adrenal effects is limited by the few modest-sized (mostly cross-sectional) studies. In contrast, the nonhuman mammalian database is more robust and can provide information on potential links between PCB exposures and changes in levels of circulating glucocorticoids and structural alterations of the adrenal cortex.

### 3.3.5. Gastrointestinal

The gastrointestinal (GI) tract is a joined series of hollow organs from the mouth to the anus, including the esophagus, stomach, small intestines, and large intestines. The GI tract, along with the liver, pancreas, and gallbladder, constitutes the digestive system. In addition to digestion, the primary functions of the GI tract include excretion, absorption, and protection from gastric acid and foreign microbes. Twenty-four studies in humans and 57 in other mammals examined GI endpoints and PCB exposure (see Figure 4); these evaluated GI histopathology or gut permeability (in nonhuman mammals), abdominal ultrasonography (in humans), and digestive system symptoms and diseases (in humans or other mammals), including specific clinical conditions (e.g., gastric ulcer and colorectal polyps) and more subjective symptoms such as abdominal pain, nausea/vomiting, changes in bowel habits, bloating, indigestion, and loss of appetite (see Figure 15). Additional endpoints reported in nonhuman mammals included intestinal bleeding, bloody stools, edema, intestinal blockage, and diverticula of the large bowel. Two human studies assessed mortality due to digestive system diseases; however, this endpoint is nonspecific and often includes liver disease (see Section 3.3.7). The most informative studies for assessing the

potential for PCB exposure to cause GI effects are those that examined GI histopathology, abdominal ultrasonography, and specific clinical conditions; remaining endpoints are often subjective or ill-defined or capture a broad range of conditions with potentially unrelated etiologies, reducing the prospect of successful integration in a systematic review.

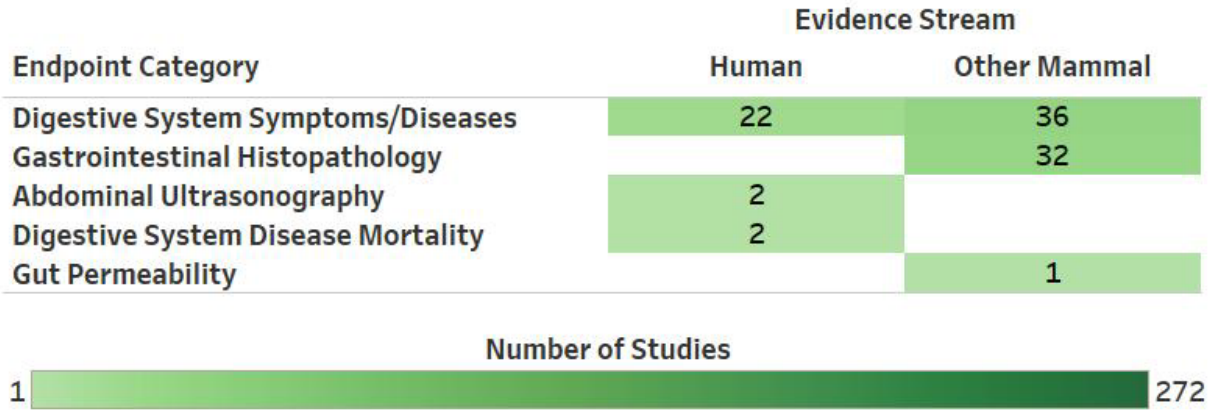


**Figure 15. Overview of Human and Other Mammalian Gastrointestinal Studies**

Summary of the database of studies evaluating exposures to PCB mixtures and gastrointestinal endpoints organized by endpoint category. Lists of studies included in each count can be accessed via the online interactive version of this figure (https://hawc.epa.gov/summary/visual/assessment/100500282/OverviewAllStudies/). Shading intensity corresponds with the number of studies in each category, from 1 to 272, which is the maximum number of nonhuman mammalian studies in any health endpoint category. The intent is to highlight not only differences in the distribution of studies across gastrointestinal endpoint categories but also to emphasize the number of gastrointestinal studies relative to the number of studies for other organs/systems.

Abdominal ultrasounds can detect abnormalities in the abdominal anatomical structure and are generally used as a diagnostic tool in patients reporting abdominal pain. Two human studies investigated PCB exposure and abdominal ultrasonography in cross-sectional studies of Yusho patients (Tokunaga and Kataoka, 2001; Hirota et al., 1995). Ultrasounds were conducted as part of an annual physical examination in Yusho patients. Both studies evaluated blood levels of PCBs and nonspecific clinical abdominal ultrasound findings. The broad categorization of the ultrasound results does not identify a specific GI endpoint and would therefore not contribute to a review of potential PCB-related GI effects. Two human studies that examined more specific clinical endpoints in general populations might be more informative. These include a case-control study that measured serum PCB levels in patients with colorectal polyps (Lee et al., 2018) and a cross-sectional study that related blood levels of PCBs to self-reported history of physician-diagnosed gastric ulcer (Nakamoto et al., 2013). These human studies ultimately provide a limited database for integration. GI symptoms and diseases evaluated in nonhuman mammals also included gastric ulcers, which were described in six studies of PCB-exposed mink and rhesus monkeys (Hornshaw et

al., 1986; Aulerich et al., 1985; Aulerich and Ringer, 1977; Allen et al., 1974a; Allen et al., 1974b; Aulerich et al., 1973).

Because of limitations of the GI endpoint data in humans, hazard identification for PCBs would likely depend on nonhuman mammalian studies of GI histopathology to help understand changes in GI structure and function that could result from PCB exposure. Fourteen studies in nonhuman primates investigated PCB exposure and gastric and intestinal histopathology (see Figure 8). These studies included evaluations of chronic, subchronic and acute exposure in adults and exposures in developing offspring (see Figure 10). GI histopathology has also been evaluated in PCB-exposed rodents and other species (see Figure 8). Furthermore, tight junction permeability of the intestinal mucosa was evaluated in one study of developmental PCB exposure in mice (Rude et al., 2019). Although studies in rodents and other species have been more limited in scope, these could provide information on variations in GI sensitivity across species. Most studies that evaluated GI histopathology exposed mammals to PCBs via the oral route (see Figure 9), but the database also includes one study of dermal exposure in rabbits (Vos and Beems, 1971) and one study of inhalation exposure in rats (Casey et al., 1999).

In summary, the existing database has limited potential to support hazard evaluation for PCB-associated GI effects. There are few epidemiological studies that have examined PCB exposure and GI endpoints. Further, most human studies meeting PECO evaluated digestive system symptoms that do not provide a strong foundation for evidence integration. However, the larger body of nonhuman mammalian studies can provide insight into more specific GI endpoints that could be further explored in human studies of PCB exposure.

### 3.3.6. Hematopoietic

Hematopoiesis describes the process by which mature blood cells are derived from stem cells along three primary lineages: erythropoiesis gives rise to red blood cells (RBCs), which carry oxygen throughout the body; lymphopoiesis produces lymphocytes, which are the cornerstone of adaptive immunity (e.g., T cells, B cells, and natural killer (NK) cells); and myelopoiesis generates cells of myeloid lineage, which are involved in innate immunity and clotting processes (e.g., granulocytes, monocytes, megakaryocytes, and platelets) (Landreth, 2005, 2002). Leukocytes, or "white blood cells" (WBCs), include lymphocytes, granulocytes, and monocytes. Hematopoietic endpoints evaluated following PCB exposure include RBC and WBC counts (overall and by type), platelet counts, hemoglobin levels, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), hematocrit levels, bone marrow histopathology, and clotting function. Many of these measures are used in clinical practice but can also be useful to detect sub- or preclinical health effects in epidemiological studies. Changes in the number or distribution of WBC types might suggest the potential for immunotoxicity. Therefore, WBC counts also are discussed in Section 3.3.8. Hematopoietic endpoints also include mortality associated with disorders/disease of the blood, although the specific codes used in these mortality studies can be ill-defined, capturing a broad range of conditions with potentially unrelated etiologies.

Changes in RBC counts, or hemoglobin can indicate the presence of anemia, which represents a decrease in the blood's oxygen transport capacity and is a significant health impact (Papanikolaou and Pantopoulos, 2017). No studies were identified that evaluated anemia per se; and, of the 14 human studies evaluating RBCs or hemoglobin (see Figure 16), all were cross-sectional, and only two were conducted in general population samples (see Figure 5). All the remaining studies were on persons occupationally exposed or with other known potential for PCB exposure. One general population study evaluated participants aged 12 years and older in the 2003–2004 cycle of the cross-sectional NHANES (Serdar et al., 2014). This study examined individual and grouped (dioxin-like and nondioxin-like) PCB congeners and RBC and WBC counts, platelet count, hemoglobin, and hematocrit. The second general population study evaluated current levels of grouped dioxin-like PCBs (TEQ [toxic equivalency] approach) and a similar set of hematopoietic parameters (thrombocytes, hemoglobin, thrombopoietin, and WBC counts) in a sample of 30 children enrolled in a birth cohort in the Netherlands (Leijs et al., 2009). Although the use of general population samples allows examination of health endpoints at relatively lower levels of exposure, the cross-sectional nature means that temporality cannot be determined; however, in the case of longer-lived PCBs measurements made at the time of the study likely represent exposure prior to outcome ascertainment. Furthermore, RBC and hemoglobin measurements were among the most common hematopoietic endpoints evaluated in nonhuman mammals following exposure to PCB mixtures, and the results of these investigations might provide additional evidence to inform an assessment of potential effects of PCB exposures on these endpoints (see Figure 16).

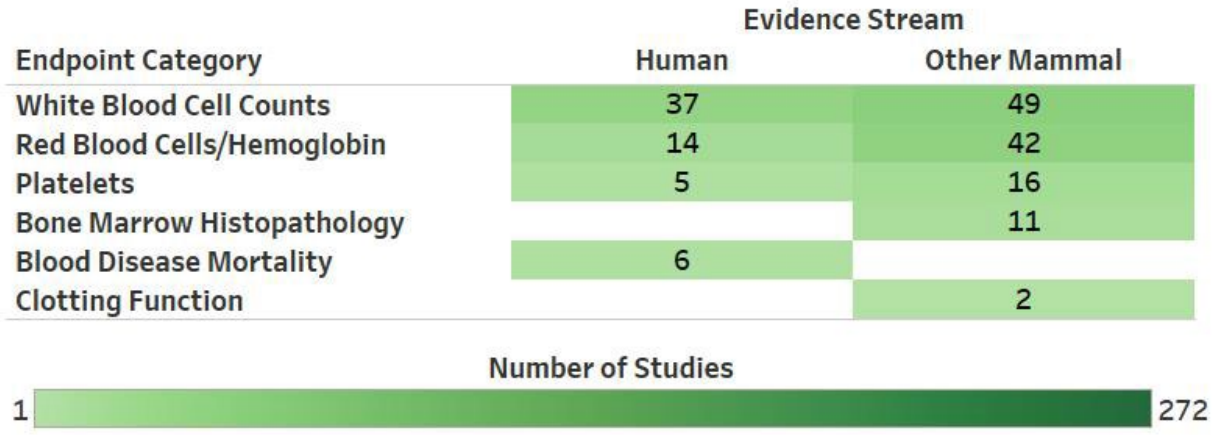


**Figure 16. Overview of Human and Other Mammalian Hematopoietic Studies**

Summary of the database of studies evaluating exposures to PCB mixtures and hematopoietic endpoints organized by endpoint category. Lists of studies included in each count can be accessed via the online interactive version of this figure (https://hawc.epa.gov/summary/visual/assessment/100500282/OverviewAllStudies/). Shading intensity corresponds with the number of studies in each category, from 1 to 272, which is the maximum number of nonhuman mammalian studies in any health endpoint category. The intent is to highlight not only differences in the distribution of studies across hematopoietic endpoint categories but also to emphasize the number of hematopoietic studies relative to the number of studies for other organs/systems.

Hemostasis is the process through which vascular integrity is restored following injury; clotting, or coagulation is a critical component of this process, vital for prevention of blood loss (Triplett, 2000). Impaired clotting function can lead to excessive bleeding; however, enhanced clotting function is also detrimental as it can lead to thrombosis and potentially life-threatening consequences (e.g., heart attack, stroke, pulmonary embolism). Platelets (or thrombocytes) are one of the primary elements of the hemostatic system. Platelet counts were measured in 5 human studies and 16 studies in other mammals (see Figure 16). However, hemostasis relies not only on the number of platelets but also on vascular endothelial cell function and the presence and function of an array of coagulation proteins. Clotting function was not assessed in any of the identified human studies of PCBs and was infrequently studied in other mammals, with only two studies evaluating this endpoint: one in rhesus monkeys (Arnold et al., 1997) and another in pigs (Platonow et al., 1976).

Of the 37 human studies of WBC counts (see Figure 16), most were cross-sectional, but there were more than ten cohort studies (see Figure 6). Eleven studies were conducted in general population samples; the remaining studies were conducted among persons either occupationally exposed or with other known potential for PCB exposure (see Figure 5). The general population samples included participants in the cross-sectional NHANES (Serdar et al., 2014; Lee et al., 2008) and birth cohorts in Sweden (Glynn et al., 2008), Norway (Stølevik et al., 2013), and Japan (Nagayama et al., 2007b). WBC counts were among the most common hematopoietic endpoints evaluated in nonhuman mammals following exposure to PCB mixtures (see Figure 16). Taken together, the human and animal data could be useful to inform an assessment of potential impacts of PCB exposure on WBC numbers, which could reflect effects on hematopoietic processes or could lead to effects on immune function (see Section 3.3.8). Information on hematopoietic processes can also be gleaned from histopathological evaluations of the bone marrow, which were conducted in 11 nonhuman mammalian studies of PCBs (see Figure 16), in both rodents and nonhuman primates (see Figure 8).

Of the six human studies evaluating mortality due to blood disease (see Figure 16), all were conducted among exposed workers and relied mainly on duration of employment as a proxy for magnitude of PCB exposure. The study populations for these analyses were sometimes overlapping but covered different time periods. Causes of death were very broad and comprise a range of conditions with potentially different etiologies: diseases of the blood and blood forming organs, other and unspecified anemia, coagulation and hemorrhagic conditions, and other disease of the circulatory system. This group of studies is considered less informative because of this broad and non-specific outcome grouping as well as use of employment duration rather than PCB exposure measured during a relevant time window.

In summary, there were numerous studies evaluating hematopoietic endpoints, including RBC, WBC, and platelet counts, as well as bone marrow histopathology (in nonhuman mammals), likely providing a sufficient foundation for evaluating hazard for these endpoints. However, there

are very few studies for endpoints related to hemostasis (e.g., clotting function), which represents an area of uncertainty that would benefit from further research.

### 3.3.7. Hepatobiliary

Hepatobiliary endpoints inform changes to the structure or function of the liver, gall bladder, bile ducts, or bile. The liver has broad and diverse biological functions, which support digestion, protein synthesis, nutrient homeostasis including glucose homeostasis, endogenous chemical and xenobiotic metabolism, and formation of bile and biliary excretion. Specifically, the liver regulates the following: protein, heme, hormone and lipid synthesis and breakdown; glycogen synthesis and availability; micronutrient storage and release; synthesis/metabolism of fats, proteins, and carbohydrates for energy; and the metabolism of other endogenous chemicals and xenobiotics. The gallbladder is a small pouch that stores bile (fluid containing cholesterol and bile acids), which is used for lipid digestion via emulsification in the small intestine. Bile is also a route of excretion for bilirubin (a byproduct of RBC recycling) and a broad range of other excretion products, including the metabolic progeny of xenobiotics and lipophilic substances themselves, including PCBs (Boyer, 2013). Responses of the hepatobiliary system to chemical exposures can range from adaptive induction of metabolic enzymes to structural or functional damage, such as cholestasis (decreased bile flow), steatosis (fatty liver), hepatitis (inflammation), necrosis (cell death), fibrosis (scarring), and cirrhosis (late-stage necrosis and fibrosis; frank liver disease). We identified 86 human and 357 other mammalian studies of PCB exposure and hepatobiliary endpoints (see Figure 4). Nonhuman mammalian models used in these studies included laboratory rodents, nonhuman primates, rabbits, mink, and other species (see Figure 8) and included exposure durations from acute to chronic, as well as developmental exposures (see Figure 10).

Of the 86 human studies of PCBs and hepatobiliary endpoints identified, only 11 included direct evaluations of liver injury, including 7 studies of deaths from cirrhosis (Kimbrough et al., 2015; Prince et al., 2006b; Prince et al., 2006a; Ruder et al., 2006; Mallin et al., 2004; Kimbrough et al., 2003; Brown and Jones, 1981) and individual studies of self-reported nonspecific liver disease (Stehr-Green et al., 1986), self-reported hepatitis (Fitzgerald et al., 1989), steatosis diagnosed from liver biopsies in bariatric surgery patients (Rantakokko et al., 2015), and ultrasonography of liver structure abnormalities in an occupational cohort of former recycling factory workers (Kaifie et al., 2019). Studies examining mortality (i.e., deaths from cirrhosis) were occupational cohort studies (Kimbrough et al., 2015; Prince et al., 2006b; Prince et al., 2006a; Ruder et al., 2006; Mallin et al., 2004; Kimbrough et al., 2003; Brown and Jones, 1981). As is common in occupational cohorts of PCB exposure, all but two of the studies used duration of employment as an exposure surrogate. In contrast, Ruder et al. (2006) and Prince et al. (2006b) used semiquantitative job exposure matrices to assign cumulative exposure categories. Despite implementing different exposure estimates, each study assessed potential relationships between PCB exposure and deaths from cirrhosis using standardized mortality ratios (SMRs). The small database of human studies with direct evaluations of liver injury can be supplemented with information from studies of other hepatobiliary endpoints

(see below) and studies of nonhuman mammals exposed to PCBs, especially those that employed histological evaluations of liver damage (see Figure 17). Nonhuman mammalian studies of PCBs also commonly evaluate the presence of lipid-containing vacuoles within hepatocytes, a sign of fatty liver [e.g., (Shi et al., 2019; Wahlang et al., 2017; Madra et al., 1995; Bergman et al., 1992; Baumann et al., 1983; Lipsky et al., 1978; Bruckner et al., 1974; Burse et al., 1974; Hansell and Ecobichon, 1974; Aulerich et al., 1973)].

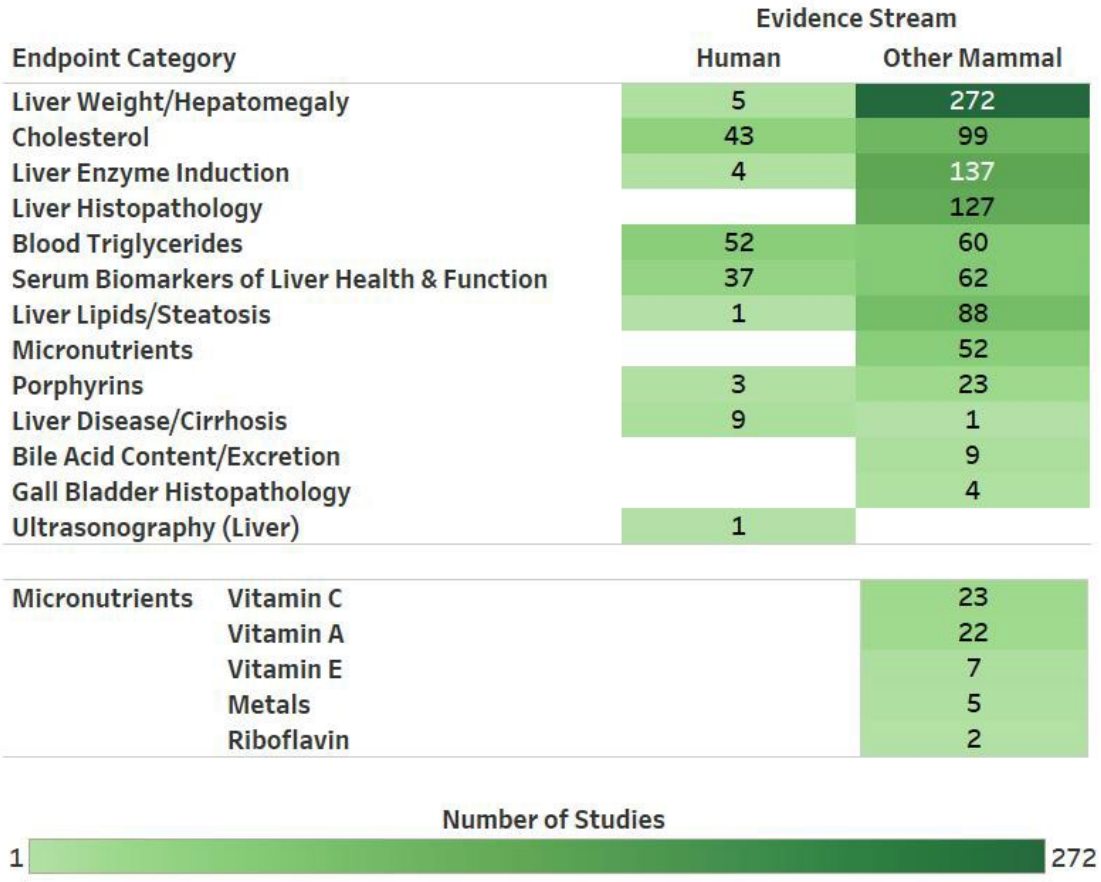


**Figure 17. Overview of Human and Nonhuman Mammalian Hepatobiliary Studies**

Summary of the database of studies evaluating exposures to PCB mixtures and hepatobiliary endpoints organized by endpoint category. Lists of studies included in each count can be accessed via the online interactive versions of this figure: (https://hawc.epa.gov/summary/visual/assessment/100500282/OverviewAllStudies/) for an overview across human and nonhuman mammalian studies; and (https://hawc.epa.gov/summary/visual/assessment/100500282/HepatobiliaryEndpointsNonhumanMammals/) for studies of nonhuman mammals only. The interactive summary of the nonhuman mammalian studies can be adjusted to group hepatobiliary endpoint categories into two levels of organization. Shading intensity corresponds with the number of studies in each category, from 1 to 272, which is the maximum number of nonhuman mammalian studies in any health endpoint category. The intent is to highlight not only differences in the distribution of studies across hepatobiliary endpoint categories but also to emphasize the number of hepatobiliary studies relative to the number of studies for other organs/systems.

Hepatomegaly (enlarged liver) can provide indirect evidence of liver damage but might also result from dysfunction in other organ systems (e.g., cardiovascular conditions). Because of this lack of specificity, studies evaluating hepatomegaly might provide stronger evidence for potential hepatobiliary effects of exposure when they also collect data on other endpoints from this system. Hepatomegaly was evaluated in four studies of Yusho patients (Kanagawa et al., 2008; Tokunaga and Kataoka, 2001; Hirota et al., 1995) or occupationally exposed workers (Maroni et al., 1980). Additionally, one other study of an occupational cohort used sonographic examination to measure liver size in PCB-exposed workers (Kaifie et al., 2019). These studies were a mix of cross-sectional and cohort studies, all of which had PCB measurements from serum or blood. Two of the five studies also evaluated serum biomarkers of liver function and health (Kaifie et al., 2019; Maroni et al., 1980). The types of serum biomarkers examined and their significance are discussed in more detail below. Like human studies of hepatomegaly, nonhuman mammalian studies of liver weight and PCB exposure can be bolstered by the inclusion of other types of data (e.g., liver histopathology or levels of serum biomarkers). Of the 272 nonhuman mammalian studies that evaluated liver weight and PCB exposure (see Figure 17), most also included evaluations of other hepatobiliary endpoints [e.g., (Wahlang et al., 2014; Oda and Yoshida, 1994; Sager, 1983; Oishi et al., 1978; Schmoldt et al., 1977; Allen et al., 1975; Bastomsky et al., 1975; Kiriyama et al., 1974; Allen et al., 1973; Vos and Notenboom-Ram, 1972)].

Many nonhuman mammalian studies evaluated endpoints that can be used to detect the induction of the xenobiotic metabolizing enzyme apparatus (see Figure 17), which is an important contributor to increased liver mass in experimental models. A robust database evaluated PCB exposures and both liver weight and markers of xenobiotic metabolism [e.g., (Arena et al., 2003; Segre et al., 2002; Aulerich et al., 1985; Saito et al., 1983a; Saito et al., 1983b; Narbonne, 1979; Bruckner et al., 1977; Grant and Phillips, 1974; Johnstone et al., 1974; Litterst et al., 1972)]. A few human studies also examined PCB exposure and drug metabolism. A small cohort study of Native American adults analyzed serum PCB levels and cytochrome P-450 1A2 (CYP1A2) (Fitzgerald et al., 2005). Activity of CYP1A2, an enzyme instrumental in drug metabolism, was estimated using a caffeine breath test to measure caffeine metabolism. Additionally, a few small occupational studies examined PCB exposure and antipyrine half-life (Emmett et al., 1988a; Krampl and Kontseková, 1978; Alvares et al., 1977).

Serum biomarkers can also be used as evidence of liver damage. For example, elevated levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) can indicate hepatocellular injury or necrosis (Lala et al., 2022; Giboney, 2005), elevated levels of bilirubin, alkaline phosphatase (ALP), or gamma-glutamyltransferase (GGT) can be associated with cholestasis (Lala et al., 2022), and cytokeratin 18 (CK18) is a validated biomarker for steatohepatitis (Feldstein et al., 2009). However, like hepatomegaly, changes in serum biomarker levels might also be related to the function of other biological systems. For example, elevated GGT can also occur with chronic heart failure, and elevated ALP can be used to detect bone disorders.

Therefore, compared to studies evaluating a single biomarker, studies evaluating these biomarkers in combination are more likely to yield hazard information specific for this organ/system. PCB exposure and levels of serum biomarkers of liver health and function, including ALT, AST, bilirubin, ALP, GGT, and CK18 were evaluated in 37 human studies (see Figure 17), many of which evaluated more than one biomarker [e.g., (Sala et al., 2001; Brown et al., 1991; Brandt-Rauf and Niman, 1988; Steinberg et al., 1986; Emmett, 1985; Fischbein, 1985; Hara, 1985; Lawton et al., 1985; Smith et al., 1982; Ouw et al., 1976)]. Most of the identified studies were cross-sectional (see Figure 6) and included PCB measurements from serum, plasma, whole blood, or adipose tissue (see Figure 7); other exposure metrics included placental PCBs (Wang et al., 2005) and generalized exposure categories based on air PCB concentrations at a capacitor manufacturing plant (Fischbein et al., 1979). Cross-sectional studies generally focused on occupational exposures or subjects in industrial areas or communities otherwise at risk for high exposure (see Figure 5). However, there were a few general population studies identified, including those using survey data from the NHANES [e.g., (Wahlang et al., 2020; Serdar et al., 2014; Christensen et al., 2013)]. In addition to cross-sectional studies, a smaller number of cohort studies examined PCBs and serum biomarker levels. These studies included mostly occupational cohorts or Yusho patients, although one was a general population study of mother-newborn pairs (Wang et al., 2005) and another was of bariatric surgery patients (Rantakokko et al., 2015). PCB exposure and biomarkers of liver health and function also were examined in 62 nonhuman mammalian studies, which can provide additional information useful for evaluating potential causal relationships between exposure and effect (see Figure 17). However, the types of histopathological changes observed with chemical exposures do not always include necrosis; therefore, it is not clear that release of liver enzymes into the blood would be among the most sensitive indicators of liver damage. Many studies in the nonhuman mammalian database evaluated serum biomarkers of liver health and function in combination with histopathological evaluations [e.g., (Wahlang et al., 2019; Wahlang et al., 2016; Wang et al., 2011; Pereira and Rao, 2006; Mayes et al., 1998; Baumann et al., 1983; Zinkl, 1977; Barsotti et al., 1976; Abrahamson and Allen, 1973; Allen et al., 1973)].

Inhibition of uroporphyrinogen decarboxylase, a key enzyme in the heme biosynthetic pathway, leads to a buildup of various uroporphyrins and increases the concentration of these products in urine. The accumulation of porphyrins is known as porphyria, and the type of porphyria caused by environmental chemicals is known as porphyria cutanea tarda. Human studies generally evaluate excretion of porphyrins in urine in individuals exposed to environmental chemicals and the relative concentrations of individual porphyrins, especially the ratio of uro- to coproporphyrins. Three human studies examined urinary porphyrins: one in individuals exposed transiently to smoke from a PCB-containing transformer fire (Osterloh et al., 1986) and two in individuals exposed occupationally during capacitor manufacture (Colombi et al., 1982; Smith et al., 1982). To supplement the data from human studies, 23 nonhuman mammalian studies measured porphyrin accumulation in liver and excretion in urine (see Figure 17).

Many fatty acids, lipids, and cholesterol are synthesized and eliminated in the liver; the relationships among them and their relevance to human health are complex (see Sections 3.3.1 and 3.3.9). Increases or decreases in serum or liver cholesterol levels can be associated with liver damage, although determining whether the changes are a consequence of that damage or a contributing factor in disease progression can be challenging (Arguello et al., 2015; Chrostek et al., 2014). Additionally, in the case of evaluating lipid-related endpoints in observational studies, reverse causality whereby lipophilic PCBs accumulate more in individuals with higher lipid levels is a possibility. PCB exposure and cholesterol levels were evaluated in 43 human studies (see Figure 17). Most of these studies used a cross-sectional design (see Figure 6), and most included PCB measurements from serum, plasma, whole blood, or adipose tissue (see Figure 7). Of the cross-sectional studies, many also investigated PCB exposures and blood triglycerides [e.g., (D'Errico et al., 2012; Uemura et al., 2009; Lee et al., 2007b; Karmaus et al., 2005; Bloom et al., 2003; Stehr-Green et al., 1986; Takamatsu et al., 1984; Chase et al., 1982; Smith et al., 1982; Baker et al., 1980)]. Similar to studies on serum biomarkers, cross-sectional studies of PCB exposure and cholesterol levels were generally conducted in occupationally exposed populations or included subjects from communities that were at high risk for exposure (see Figure 5). A few general population studies included those conducted using national survey data, such as NHANES (Patel et al., 2012; Lee et al., 2007b). Additionally, four of the cross-sectional studies were focused on children of various ages (including studies of infants, school children, and teenagers) (Nakamoto et al., 2013; Karmaus et al., 2005; Schell et al., 2004; Kreiss et al., 1981). Notably, six prospective studies examined PCB exposure and cholesterol and triglyceride levels in children (Güil-Oumrait et al., 2021; Su et al., 2012), young adults (Suarez-Lopez et al., 2019; Lee et al., 2011), or older adults (Stubleski et al., 2018; Penell et al., 2014). In addition to providing evaluations of general populations at lower PCB levels, the longitudinal nature of these studies might address the potential for reverse causality, as discussed previously. Finally, a subset of studies of occupational cohorts or Yusho patients also examined PCBs and cholesterol or triglyceride levels using a longitudinal design (Gaum et al., 2019; Kaifie et al., 2019; Kimáková et al., 2018; Tokunaga and Kataoka, 2003; Hirota et al., 1993b; Hirota et al., 1993a; Brown et al., 1991; Murai et al., 1987; Fitzgerald et al., 1986; Hara, 1985). PCB exposures and cholesterol or triglyceride levels also were examined in 99 and 60 nonhuman mammalian studies, respectively; data collected following controlled exposures in animals can provide additional information useful for evaluating potential causal relationships between exposure and effect (see Figure 17). As discussed in Section 3.3.1and Section 3.3.9, elevated blood levels of cholesterol or triglycerides are considered important risk factors for cardiovascular disease and type 2 diabetes mellitus (T2D).

The liver also plays an important role in nutrient homeostasis, regulating micronutrient storage and release. Fifty-two nonhuman mammalian studies explored PCB exposure and liver levels of micronutrients, including vitamin A (retinoids), vitamin C (ascorbic acid), vitamin E (alpha-tocopherol), vitamin B2 (riboflavin), zinc, calcium, copper, iron, magnesium, potassium,

manganese, and selenium (see Figure 17). Vitamin A is stored in the liver, primarily in specialized fat storing cells, in the form of retinyl palmitate, and an equilibrium exists with blood by which vitamin A as retinol is delivered to tissues. Twenty-two nonhuman mammalian studies explored PCB exposures and the dynamics of vitamin A storage, distribution, metabolism, and excretion (see Figure 17). Twenty-three studies of PCBs in mammals other than humans assessed water-soluble vitamin C, while seven evaluated lipid-soluble vitamin E. These studies were well designed to ascertain possible adverse effects. The liver is also a principal storage site for several metals, including zinc, calcium, copper, iron, magnesium, potassium, manganese, and selenium. Five studies described PCB exposures and distribution of these metals within the liver and the activity of enzymes that contain them, especially important antioxidant enzymes, like Cu/Zn superoxide dismutase, Mn superoxide dismutase, Se-dependent glutathione peroxidases and others. Investigations of metals in the liver also can have important implications for other organ systems; for example, calcium metabolism can influence bone and tooth health and development (see Section 3.3.10).

Four studies have investigated gallbladder and biliary duct histopathology in nonhuman primates (see Figure 17). However, experimental studies of PCB exposure often use rats (see Figure 8), which have no gallbladder, and this could have contributed to a general lack of attention to this organ. In addition to potential changes in bile duct morphology, bile content and flow rate can also reflect liver status and health. Bile acid content and excretion of bile have been evaluated in nine studies of rats exposed to PCB mixtures (see Figure 17).

In summary, the human database of PCB exposure and hepatobiliary endpoints contains only a few studies that directly evaluate liver injury, and those consist mostly of prospective studies on cirrhosis mortality in occupational cohorts. Most available human studies were cross-sectional analyses, particularly those evaluating serum biomarkers of liver function or cholesterol or triglyceride levels. Particularly in the case of lipid measurements, where the potential for reverse causality is significant, cross-sectional studies are limited in that they do not establish temporality between the exposure and outcome (see Section 3.2.1). However, there is a robust database of nonhuman mammalian studies to inform temporality between PCB exposures and these endpoints at a wide range of exposure levels. Animal studies also have evaluated PCB exposures and a broad range of structural and functional parameters of the liver. Therefore, the overall database likely provides sufficient information to draw hazard conclusions for hepatobiliary endpoints and PCB exposure. Additional prospective human studies, including more studies in nonoccupational cohorts, might strengthen the database, while PCB exposure and gallbladder and biliary endpoints represent an area of uncertainty that would benefit from further research.

### 3.3.8. Immune

The immune system is highly dispersed, comprising multiple organs, tissues, and cell types, the main function of which is to ensure homeoregulatory maintenance by preventing or limiting infection and malignancy (IPCS, 2012). Adverse effects can result from suppression of the immune

system, which can lead to reduced antibody production, greater infectious morbidity, and poorer surveillance of tumor producing cells. Inappropriate stimulation, as is the case with allergy and atopic disease, or inappropriate recognition of self-antigen, in the case of autoimmunity, can also result from immune dysregulation. Immune endpoints can be grouped based on proposed mechanistic pathways of immunosuppression, hypersensitivity, and autoimmunity. For this review, endpoints included in this domain are as follows: susceptibility to infection/malignancy, atopy (i.e., allergy and asthma), autoimmune disease, antigen-specific antibody responses (e.g., to vaccination), WBC function, delayed-type hypersensitivity (DTH) responses, antibody levels, immune organ size and weight, immune organ histopathology, and endotoxin sensitivity. WBC counts are considered briefly here, but these can also reflect effects on hematopoietic processes and are discussed primarily in Section 3.3.6. With respect to identifying hazards from chemical exposures, the most informative immune endpoints are those that measure a change in immune function in response to challenge, such as susceptibility to infection, atopy, autoimmune disease, antigen-specific antibody responses, WBC function (e.g., lymphocyte proliferation assays, NK cell activity assays), and DTH. These endpoints have been routinely measured in epidemiological studies and in clinical settings. Other immune endpoints might be less sensitive or less reliable indicators of significant and persistent effects on immune function (e.g., WBC counts, immunoglobulin [Ig]) levels, immune organ size/weight, immune organ histopathology, and endotoxin sensitivity) (IPCS, 2012). Because of the potential lack of sensitivity and specificity of these endpoints, studies evaluating these in combination, especially alongside more informative measures of immune function, might provide greater evidence for meaningful health implications compared with studies that evaluate only one of these endpoints in isolation.

One hundred and five human and 131 other mammalian studies evaluated PCB exposure and immune endpoints; many of these included multiple assays (see Figure 4). Most human studies of immune endpoints used biomarkers to characterize PCB exposure, with varying numbers of PCB congeners measured in blood or breast milk (see Figure 7). Less commonly, PCBs were measured in sputum (Nakanishi et al., 1985; Shigematsu et al., 1978), adipose tissue (Chase et al., 1982), umbilical cord tissue (Ochiai et al., 2014), or placental tissue (Reichrtová et al., 1999), or characterized using dietary assessment (Stølevik et al., 2013; Stølevik et al., 2011; Svensson et al., 1994). In some cases, occupational exposure was inferred based on work history rather than biospecimens or biomonitoring (Kimáková et al., 2018; Parker-Lalomio et al., 2018; Kimbrough et al., 2015; Mallin et al., 2004; Langer et al., 2002; Osterloh et al., 1986). Nonhuman mammalian studies of PCBs and immune endpoints have been conducted most frequently in laboratory rodents, rabbits, and nonhuman primates, but some studies have also used mink or livestock (see Figure 8). Study designs include exposure durations from acute to chronic and multigenerational studies evaluating endpoints following exposures during critical developmental periods (see Figure 10); for the immune system, these include prenatal and postnatal periods through adolescence (Dietert et al., 2000).

One endpoint with clear relevance for immune function is the occurrence of infectious disease, as evaluated in 31 human studies (see Figure 18), mainly prospective cohorts (see Figure 6). Many studies relied on questionnaires of the participant (or parent) to ascertain outcomes, which could lead to outcome misclassification. However, some studies in the database used other methods such as medical chart review [e.g., (Dallaire et al., 2006; Dallaire et al., 2004)], which would alleviate misclassification to some degree. The bulk of the studies focused on the following: respiratory disease (upper or lower respiratory tract infection (Gascon et al., 2014b; Stølevik et al., 2013; Gascon et al., 2012; Stølevik et al., 2011; Sunyer et al., 2010; Glynn et al., 2008; Dallaire et al., 2006; Dallaire et al., 2004; Weisglas-Kuperus et al., 2004; Rogan et al., 1987; Shigematsu et al., 1978); rhinitis, bronchitis, or tonsillitis (Gascon et al., 2014a; Sunyer et al., 2010; Mallin et al., 2004; Yu et al., 1998; Weisglas-Kuperus et al., 1995); pneumonia (Kimbrough et al., 2015; Sunyer et al., 2010; Mallin et al., 2004; Weisglas-Kuperus et al., 2004; Weisglas-Kuperus et al., 2000); influenza (Yu et al., 1998); cold symptoms (Liebl et al., 2004; Hara, 1985); or otitis media (Parker-Lalomio et al., 2018; Jensen et al., 2013; Stølevik et al., 2013; Stølevik et al., 2011; Dallaire et al., 2006; Dallaire et al., 2004; Weisglas-Kuperus et al., 2004; Dewailly et al., 2000; Weisglas-Kuperus et al., 2000; Yu et al., 1998; Chao et al., 1997; Weisglas-Kuperus et al., 1995; Rogan et al., 1987)). Fewer studies evaluated a range of other infectious diseases (gastrointestinal infection (Henríquez-Hernández et al., 2015; Stølevik et al., 2013; Stølevik et al., 2011; Dallaire et al., 2004; Yu et al., 1998; Rogan et al., 1987), chicken pox (Stølevik et al., 2013; Stølevik et al., 2011; Weisglas-Kuperus et al., 2004; Weisglas-Kuperus et al., 2000), and other diseases (Arisi et al., 2021; Karmaus et al., 2005; Weisglas-Kuperus et al., 2004; Van Den Heuvel et al., 2002; Weisglas-Kuperus et al., 2000)). The human database is supplemented by studies that used rodent models of host resistance to tumor challenge (Lubet et al., 1986; Loose et al., 1981; Kerkvliet and Kimeldorf, 1977) and to infectious agents such as *Plasmodium berghei* (malaria) (Loose et al., 1979; Loose et al., 1978a; Loose et al., 1978b), *Salmonella typhimurium* (Thomas and Hinsdill, 1978), *Listeria monocytogenes* (Lubet et al., 1986), *Staphylococcus aureus* (Imanishi et al., 1984), herpes simplex virus (Imanishi et al., 1980), ectromelia virus (Imanishi et al., 1980), and influenza virus (Imanishi et al., 1984). Six studies evaluated PCB exposure and bacterial endotoxin sensitivity in mice and rats (see Figure 18). Endotoxin is a lipopolysaccharide found in the cell wall of gram-negative bacteria that can trigger a strong inflammatory response, leading, in some cases, to sepsis and septic shock (Opal, 2010). Endotoxin sensitivity can have significant implications for susceptibility to and ability to recover from gram-negative bacterial infections. Of the six studies that measured endotoxin sensitivity, four also evaluated susceptibility to infection (Loose et al., 1979; Loose et al., 1978a; Loose et al., 1978b; Thomas and Hinsdill, 1978), although only one (Thomas and Hinsdill, 1978) included infection with gram-negative bacteria (*S. typhimurium*).

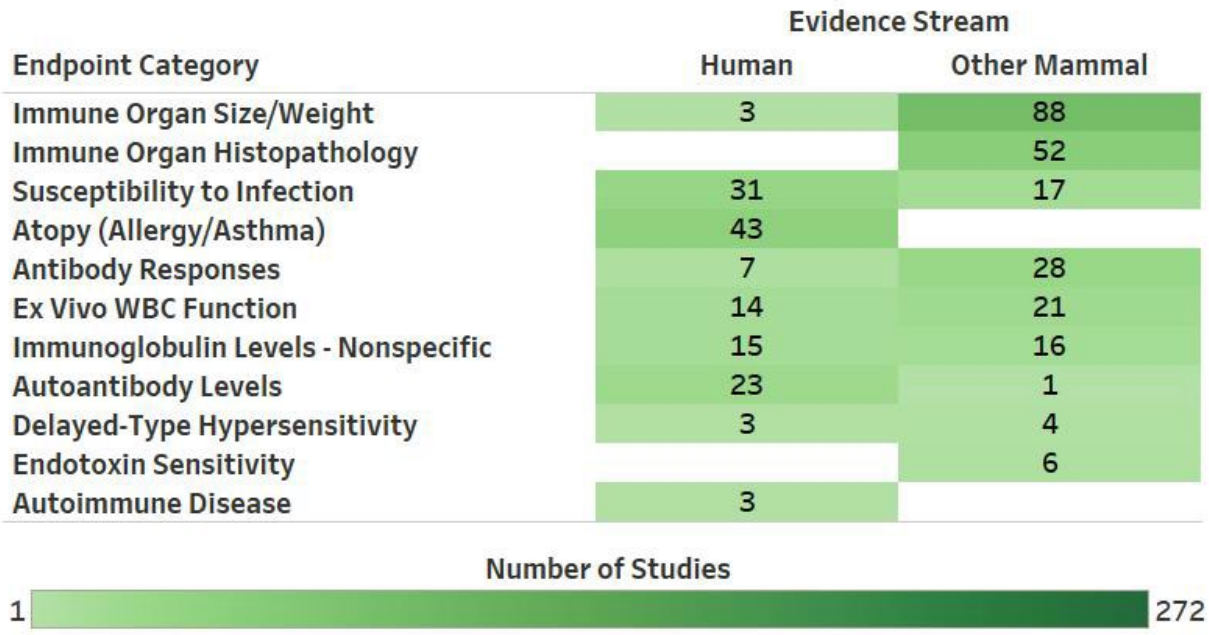


**Figure 18. Overview of Human and Other Mammalian Immune Studies**

Summary of the database of studies evaluating exposures to PCB mixtures and immune endpoints organized by endpoint category. Lists of studies included in each count can be accessed via the online interactive version of this figure (https://hawc.epa.gov/summary/visual/assessment/100500282/OverviewAllStudies/). Shading intensity corresponds with the number of studies in each category, from 1 to 272, which is the maximum number of nonhuman mammalian studies in any health endpoint category. The intent is to highlight not only differences in the distribution of studies across immune endpoint categories but also to emphasize the number of immune studies relative to the number of studies for other organs/systems. WBC = white blood cell.

The production of antigen-specific antibodies in response to an immune challenge is a sensitive and specific measure of immune function that is relatively easy to quantify in both humans and other mammals, making it highly informative for the identification of immune hazards, especially those resulting in immune suppression (IPCS, 2012). Seven human studies conducted in prospective birth cohorts evaluated vaccine-specific antibody levels among children born in the Netherlands (Weisglas-Kuperus et al., 2000), Norway (Støvelik et al., 2013), the Faroe Islands (Heilmann et al., 2010; Heilmann et al., 2006) Greenland (Timmermann et al., 2021), and eastern Slovakia (Jusko et al., 2016; Jusko et al., 2010). Five of these reported antibody responses to tetanus or diphtheria vaccines (Timmermann et al., 2021; Støvelik et al., 2013; Heilmann et al., 2010; Jusko et al., 2010; Heilmann et al., 2006). Two studies evaluated response to measles and rubella vaccination (Støvelik et al., 2013; Weisglas-Kuperus et al., 2000). Other vaccine responses evaluated included anti-*Haemophilus influenzae* type b (Støvelik et al., 2013; Jusko et al., 2010), anti-*Mycobacterium bovis* bacille Calmette–Guérin (BCG, the vaccine for tuberculosis) (Jusko et al., 2016), and mumps (Weisglas-Kuperus et al., 2000). In most cohorts, PCB exposure was characterized using biosamples taken from the mother or offspring (see Figure 7), while one (Støvelik et al., 2013) used reported maternal dietary intake to estimate exposure. Antigen-specific

antibody responses have also been evaluated in 28 nonhuman mammalian studies (see Figure 18), including studies in rhesus monkeys that evaluated antibody responses to sheep red blood cells after several years of oral exposure to PCBs in adult females (Tryphonas et al., 1991; Tryphonas et al., 1989) and perinatal exposure in their offspring (Arnold et al., 1995).

Although the integrity of the immune system is maintained within its major organs (e.g., bone marrow, spleen, thymus, lymph nodes), its effector functions occur primarily through the actions of individual cells. For this reason, many assays of immune function are based on measurements of WBC function (e.g., NK cell activity, mixed leukocyte reaction (MLR), lymphocyte proliferation assays, phagocytosis assays). These assays have been found predictive for immune suppression, especially when used in combination, and have concordant results (Luster et al., 1992). Fourteen human studies, many of which were cross-sectional, evaluated WBC function (see Figure 18, Figure 6). A few cohort studies were conducted among populations of postmenopausal women (Spector et al., 2014), occupationally exposed workers (Haase et al., 2016), and one prospective birth cohort (Belles-Isles et al., 2002). All three of these included measures of NK cell activity and T cell responses to mitogenic stimulation, with Haase et al. (2016) also measuring the ability of WBCs to phagocytize and kill bacteria via oxidative burst. Twenty-one studies conducted in PCB-exposed mice, rats, rabbits, and nonhuman primates evaluated WBC functions including NK cell activity, MLR, cytotoxic T lymphocyte activity, phagocytic activity, macrophage superoxide production, lymphocyte proliferation in response to mitogenic stimulation, and cytokine production (see Figure 18, Figure 8). Of these 21 studies, all but 5 (Smith et al., 2003; Nakanishi et al., 1995; Talcott et al., 1985; Carter and Clancy, 1980; Bonnyns and Bastomsky, 1976) evaluated multiple assays of WBC function or a single assay of WBC function in combination with some other measure of immune function (e.g., host resistance, antigen-specific antibody responses, DTH).

Like assays of WBC function, the DTH response has been found to be useful for predicting immune suppression, especially when evaluated in combination with other assays of immune function (Luster et al., 1992). Three studies evaluated DTH among Yu-Cheng patients (Wu et al., 1984a; Wu et al., 1984b; Chang et al., 1981), comparing exposed patients to unexposed individuals matched for age and sex. However, findings from these studies are limited by the potential for selection bias and the inability to separate potential effects of the PCBs themselves from effects of their degradation products, especially PCDFs (see Section 3.2.1). Four studies in laboratory mammals exposed to PCBs evaluated DTH responses to agents including oxazolone [one study in mice (Talcott and Koller, 1983)], dinitrofluorobenzene [one study in rabbits (Thomas and Hinsdill, 1980)], and tuberculin [one study in rabbits (Street and Sharma, 1975) and one in guinea pigs (Vos and Van Driel-Grootenhuis, 1972)]. All four of these studies evaluated DTH in combination with other measures of immune function.

Forty-three human studies evaluated PCB exposure and endpoints related to allergy or asthma (see Figure 18). The most informative studies in this database evaluated clinical diagnoses of asthma. One investigation, reported across two publications (Meng et al., 2016a; Meng et al.,

2016b), ascertained asthma via doctor's examination, while another (Hansen et al., 2014) inferred asthma on the basis of asthma medication use from a medical registry. Other studies focused on infants or children and evaluated dermal (e.g., eczema) or respiratory (e.g., wheeze, cough, congestion, or shortness of breath) symptoms and self-/parent-reported occurrence of allergy or asthma. Overall, the numerous studies conducted with a variety of study populations should allow identification of potential hazard. Furthermore, studies of allergy and asthma cases are supplemented by studies that measured allergen specific IgE antibodies, including studies of prospective birth cohorts in Demark (Hansen et al., 2015) and the Faroe Islands (Grandjean et al., 2010), a cross-sectional study of Flemish adolescents (Van Den Heuvel et al., 2002), and a study of asthmatic and nonasthmatic children in Japan (Tsuji et al., 2012). These studies measured levels of IgE specific for a wide variety of allergens, including dust mites, animal danders, grasses, molds, trees, pollen, egg, milk, and wheat.

Among the human studies of autoimmune dysfunction, occurrence of autoimmune disease—as evaluated in three human studies—could be more informative compared with autoantibody levels (n = 23) (see Figure 18). One study examined arthritis in a cross-sectional sample of the general US population (NHANES) (Lee et al., 2007c); the analyses specific to rheumatoid arthritis among women are relevant to evaluating potential immune hazard, while analyses of osteoarthritis are discussed elsewhere (see Section 3.3.10). A second study was a case-control analysis of type 1 diabetes (Rignell-Hydbom et al., 2010), which was constructed from a biobank of maternal serum samples and thus had prenatal measures of PCB 153. The last study, conducted among occupationally exposed workers, evaluated both autoimmune disease and autoantibody titers (Schoenroth et al., 2004). In total, 23 studies, including Schoenroth et al. (2004), evaluated autoantibody titers (see Figure 18). Many evaluated thyroid antibody levels (e.g., anti-thyroid peroxidase)[e.g., (Benson et al., 2018; Gaum et al., 2016; Brucker-Davis et al., 2011; Langer et al., 2009; Schell et al., 2009; Langer et al., 2007a; Langer et al., 2005; Langer et al., 2003; Langer et al., 2002; Murai et al., 1987)], which have also been measured in one study of PCB-exposed rats (Gu et al., 2009); thyroid hormone levels are discussed in Section 3.3.4. Most of the human studies of autoantibody titers were cross-sectional (see Figure 6), limiting inference; however, one study (Osuna et al., 2014) was based on a prospective cohort, evaluating IgM and IgG autoantibody levels in children born in the Faroe Islands, while two other studies evaluated thyroid autoantibodies, one in Yusho patients (Murai et al., 1987) and one in a medical surveillance study with repeated evaluations (Gaum et al., 2016). Thus, there are few data available to inform potential associations of PCB exposure with autoimmune disease, but more data are available for the less specific endpoint of autoantibody levels.

Although considered less informative endpoints due to their nonspecific nature, several studies evaluated WBC counts (see Section 3.3.6) or nonspecific antibody levels (15 human and 16 other mammalian studies) (see Figure 18). In addition, three human studies measured immune organ size—two evaluated thymus volume in the same cohort of children born to mothers living in

eastern Slovakia (Jusko et al., 2012; Park et al., 2008), and one evaluated splenomegaly in Yusho patients (Hirota et al., 1995). Immune organ weight and histopathology have been evaluated extensively in PCB-exposed mammals other than humans (88 and 52 studies, respectively) (see Figure 18). Although not as sensitive and specific as measures of immune function, these endpoints can be useful for supporting hazard conclusions.

Overall, information available to draw hazard conclusions for immune endpoints and PCB exposure is sufficient, especially with regard to immune suppression, which can be supported by studies of highly informative endpoints, such as susceptibility to infection/malignancy, antigen-specific antibody responses, WBC function, and DTH responses. The database also has some potential to support conclusions about PCB exposure and allergies/asthma. However, scant data are available on PCBs and autoimmunity, representing an area of uncertainty that would benefit from further research.

### 3.3.9. Metabolic

For this review, metabolic endpoints include measures related to glucose metabolism and overweight/obesity (OW/OB). Measures related to glucose metabolism evaluated in combination with PCB exposure in humans include the following (see Figure 19): insulin resistance (IR); impaired glucose tolerance (IGT)/prediabetes; T2D; gestational diabetes; diabetes mellitus not otherwise specified (DM NOS); and metabolic syndrome (MetS). Diabetic nephropathy is a renal complication of DM discussed in Section 3.3.15. The most common metabolic endpoints evaluated in humans were OW/OB and DM NOS. Sixty-nine published articles (see Figure 4) reporting the results of studies in laboratory mammals exposed to PCB mixtures have evaluated metabolic endpoints such as increases in body weight/adiposity, markers of glucose homeostasis, and basal metabolic rate (see Figure 19). Most of these studies were conducted in rats, followed by mice, rhesus or cynomolgus monkeys, and other species (see Figure 8).

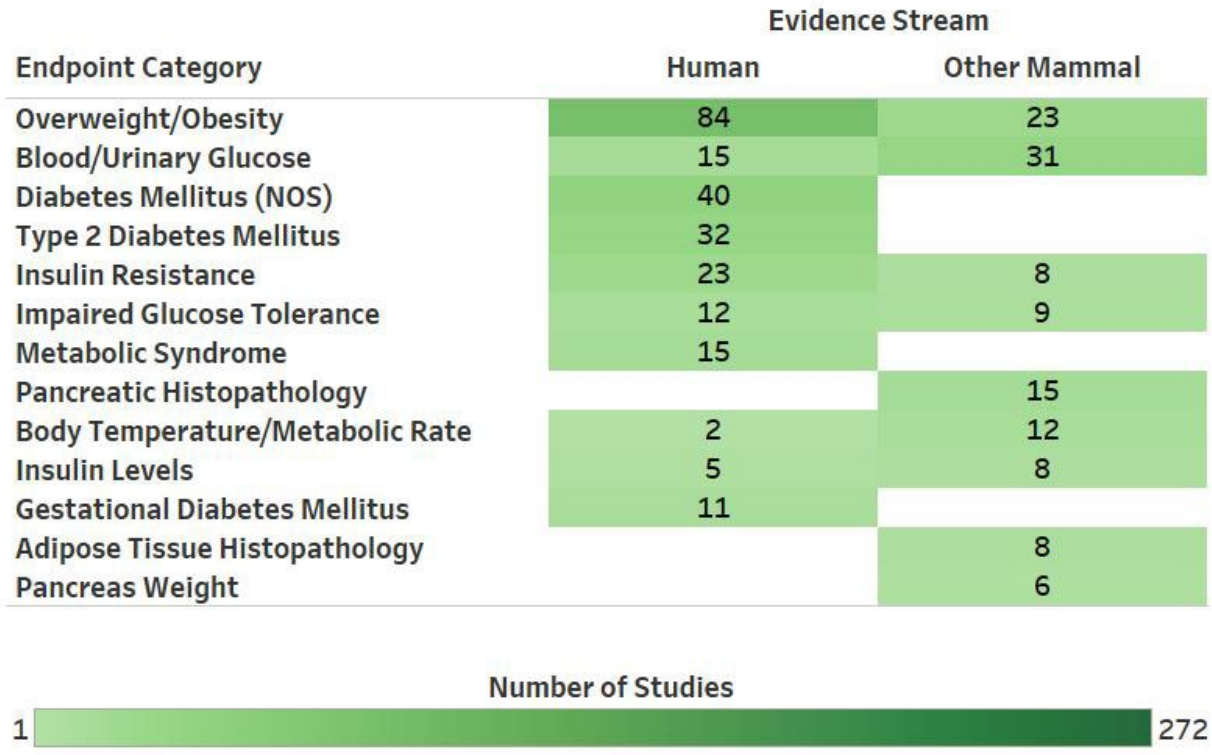


**Figure 19. Overview of Human and Other Mammalian Metabolic Studies**

Summary of the database of studies evaluating exposures to PCB mixtures and metabolic endpoints organized by endpoint category. Lists of studies included in each count can be accessed via the online interactive version of this figure (https://hawc.epa.gov/summary/visual/assessment/100500282/OverviewAllStudies/). Shading intensity corresponds with the number of studies in each category, from 1 to 272, which is the maximum number of nonhuman mammalian studies in any health endpoint category. The intent is to highlight not only differences in the distribution of studies across metabolic endpoint categories but also to emphasize the number of metabolic studies relative to the number of studies for other organs/systems. NOS = not otherwise specified.

All the endpoints mentioned above are closely related on a pathophysiological basis, primarily via visceral obesity and IR. OW/OB facilitates the development of IR. The progression of IR results in glucose homeostasis dysregulation further advancing to clinically significant and detectable glucose intolerance and T2D. Development of IR during pregnancy can progress to gestational DM (DM diagnosed during pregnancy in women without prior DM, which resolves after delivery). IR also plays a key role in the pathogenesis of MetS. MetS is a complex pathophysiological state composed of causally interrelated conditions that increase the risk of T2D and cardiovascular disease: OW/OB; IR; hypertension; high triglyceride levels; and low high-density lipoprotein (HDL) cholesterol levels. As discussed below, the combinations of these conditions used as diagnostic criteria vary slightly per various definitions of MetS. Studies of PCB exposure and cardiovascular disease and hypertension are discussed in Section 3.3.1; triglyceride and cholesterol levels are included in Section 3.3.7.

The most informative metabolic endpoints for supporting hazard identification include markers of glucose homeostasis and gestational diabetes. IR, IGT, and T2D are particularly informative because glucose homeostasis/IR is a pathophysiological continuum, all stages of which can be verified using standard clinical laboratory tests. However, the accuracy of specific methods used for evaluating metabolic endpoints in humans varies. For IR, the better measures are the ones calculated on the basis of insulin and glucose blood levels, such as homeostasis model assessment-IR (HOMA-IR) and insulin sensitivity index (ISI-gly), both of which were investigated in cohort and case-control studies of PCBs [e.g., (Park et al., 2016; Suarez-Lopez et al., 2015; Tang-Péronard et al., 2015)] and in cross-sectional studies (Arrebola et al., 2015; Jensen et al., 2014). For IGT/preDM, the preferred measure is a laboratory test of impaired fasting glucose (IFG); this method was used only in cross-sectional studies of PCB-exposed populations [e.g., (Jorgensen et al., 2008; Langer et al., 2007a)]. For T2D, the better measures include lab tests based on plasma glucose concentration, a diagnosis of T2D by a physician, or treatment with antidiabetic medications other than insulin. Several studies investigating PCBs and T2D using preferred endpoint measures were conducted as cohort and case-control studies [e.g., (Rylander et al., 2015; Lee et al., 2010; Rignell-Hydbom et al., 2009a; Turyk et al., 2009)]; others used a cross-sectional design [e.g., (Faerch et al., 2012; Tanaka et al., 2011)]. Gestational diabetes has been evaluated in relatively few studies of PCBs but is likely diagnosed more completely than other metabolic endpoints due to use of routine screening during prenatal care. Four cohort studies (Rahman et al., 2019; Vafeiadi et al., 2017; Valvi et al., 2017; Shapiro et al., 2016) and five case-control studies (Alvarez-Silvares et al., 2021; Liu et al., 2021; Liu et al., 2019; Zhang et al., 2018; Eslami et al., 2016) used preferred measures (laboratory tests, diagnosis at a hospital) to define gestational diabetes, while one cohort study (Jaacks et al., 2016) and one cross-sectional study (Neblett et al., 2020) used self-reporting to define gestational diabetes.

In addition to the rich database of human studies of PCB exposure and glucose homeostasis, a substantial database of nonhuman mammalian studies evaluating related endpoints is available, including blood and urinary glucose levels, blood insulin levels, IR, and IGT (see Figure 19). The most informative studies are likely those that evaluated IR or IGT; all were conducted in mice (see Figure 8). Of the 8 studies evaluating blood insulin levels, 7 were conducted in mice and 1 in rats (see Figure 8). Blood and urinary glucose levels were evaluated in a wide variety of species, including mice, rats, nonhuman primates, mink, and dogs (see Figure 8); two of these studies assessed glucose levels following gestational and lactational PCB exposure in rats (Dziennis et al., 2008; Chu et al., 2005), and one evaluated cynomolgus monkey infants exposed directly from birth to 20 weeks of age (Arnold et al., 1999). This database can be used to supplement the data from human studies. Furthermore, pancreas weight and histopathology have also been evaluated in PCB-exposed mice, rats, nonhuman primates, mink, rabbits, and guinea pigs (see Figure 8). Studies in nonhuman mammalian models might also provide insights into sex dependency of potential responses to PCB exposure. Some studies of laboratory mammals exposed to PCBs have compared

endpoints including IR and pancreatic histopathology in males and females [e.g., (Wahlang et al., 2019)].

Metabolic endpoints that are less informative for hazard identification include MetS, DM NOS (diabetes mellitus, not otherwise specified), and OW/OB. Several different sets of MetS diagnostic criteria have been used in the past two decades (since 1998), impeding the comparison of results across different studies, and a designated ICD-9 code was not approved for MetS until 2001. However, the same set of five components – OW/OB, IR/IGT, hypertension, elevated triglycerides, and decreased HDL cholesterol – is used by all MetS definitions, and because all five MetS components are pathophysiologically interrelated and strongly associated, use of different criteria across studies does not dismiss the existence of MetS when it is reported in those studies, but rather emphasizes different aspects of its clinical manifestations. Fifteen human studies evaluated MetS and PCB exposure (see Figure 19), including 5 cohort studies in adults of varying age ranges (Lind et al., 2017; Mustieles et al., 2017; Dirinck et al., 2016; Lee et al., 2011) or preadolescents (Lee et al., 2016), as well as a nested case-control study of adults free of MetS at baseline (Lee et al., 2014).

DM NOS is the broadest diagnostic category for diabetes (a "top" ICD code that has no "parent" code: ICD-9 three-digit code 250) encompassing all types of DM, including type 1 DM (T1D), which is caused by autoimmune destruction of beta-cells in the pancreas (the immunological mechanism) rather than by IR (the metabolic mechanism of T2D and gestational DM). Studies explicitly evaluating T1D are addressed in Section 3.3.8 However, because about 90% of individuals with DM have T2D, DM NOS, although much less accurate, is still usable, and cohort and case-control studies of PCB exposure and DM NOS have been conducted (see Figure 6). Overall, 40 studies of PCB exposure and DM NOS are available, including DM NOS mortality (see Figure 19). The better measures of DM NOS are lab tests, a record of antidiabetic medications in an administrative database, a diagnosis of DM in a hospital discharge record, or a death record (for DM NOS mortality), as used in several studies of PCB exposure [e.g., (Nakamoto et al., 2013; Ukropec et al., 2010; Mallin et al., 2004)].

OW/OB is multifactorial and highly prevalent in the general population, which can make detecting associations with chemical exposures challenging. However, this is the most commonly evaluated metabolic endpoint in the database of human PCB studies, and preferred measures of OW/OB (i.e., body mass index [BMI] and waist circumference) have been used in cohort and case-control studies of PCB exposure [e.g., (Agay-Shay et al., 2015; Vafeiadi et al., 2015)]. Also, 23 nonhuman mammalian studies have focused on PCB exposures and increases in body weight and adiposity (see Figure 19). These studies were conducted in mice, rats, mink, and nonhuman primates (see Figure 8). Adiposity has been estimated using measures of body weight and BMI and direct measures of the size of specific adipose tissue depots. Notably, at least one study in mice (Xi et al., 2019) evaluated adiposity using visceral fat somatic index (visceral fat weight/body weight), which is a particularly relevant measure because of the association in humans between visceral

adipose tissue mass and the development of insulin resistance and T2D (Bjørndal et al., 2011). There are also eight studies of adipose tissue histopathology in mice, rats, and Yorkshire piglets (see Figure 19, Figure 8), and four studies of OW/OB in rats and mice measured blood leptin levels (Jin et al., 2020; Wahlang et al., 2019; Wahlang et al., 2016; Provost et al., 2007). Leptin is an adipokine, which is primarily secreted by adipocytes, and acts by suppressing hunger and food intake and increasing energy expenditure (Stern et al., 2016).

Basal metabolic rate has been evaluated in 12 studies in species including mice, rats, cats, and Holstein cattle (see Figure 19, Figure 8). Measures of basal metabolic rate used in these studies include oxygen consumption, carbon dioxide production, respiratory exchange rate, total energy expenditure, and body temperature. These observations could be used to supplement the information reported by studies of other metabolic endpoints in humans and other mammals.

In summary, the human and other mammalian databases are likely to provide enough information to evaluate the potential for PCB-associated metabolic effects, including effects on glucose metabolism and overweight/obesity.

### 3.3.10. Musculoskeletal

The musculoskeletal system consists of the bones, teeth, muscles, joints, cartilage, and other connective tissues that support the body, allow for movement, and protect vital organs. Musculoskeletal endpoints, including measures of bone strength and density, bone histopathology, bone development, dentition, skeletal muscle histopathology, muscle mass and tone, and arthritis have been evaluated in the context of PCB exposure. Of the 30 human studies identified (see Figure 4), 10 examined musculoskeletal complaints and diseases (see Figure 20), including only subjective endpoints such as muscle and joint pain and muscle weakness. Because these studies captured a broad range of nonspecific conditions with potentially unrelated etiologies, they are of limited use for supporting conclusions about potential causal relationships between PCB exposure and specific musculoskeletal endpoints. Most of the remaining human studies evaluated bone strength and density and dental abnormalities, which are critical to overall health and quality of life (see Figure 20). An adverse effect on bone strength and density can increase the risk of fractures, which is an important public health concern due to its related morbidity, mortality, and diminished quality of life (HHS, 2000). Similarly, poor dental health can lead to periodontal disease and tooth decay, which have been associated with systemic health conditions such as cardiovascular disease (Mayo Clinic, 2021; Evans, 2009). A few studies evaluated PCB exposure and bone age and arthritis, including rheumatoid arthritis, which is an autoimmune condition also considered in Section 3.3.8 (see Figure 20). Through controlled experiments, 23 studies in nonhuman mammalian models (see Figure 4), including mice, rats, rabbits, mink, swine, and nonhuman primates (see Figure 8), assessed PCB exposure and bone density, development, and histopathology, as well as dental abnormalities and skeletal muscle histopathology (see Figure 20).

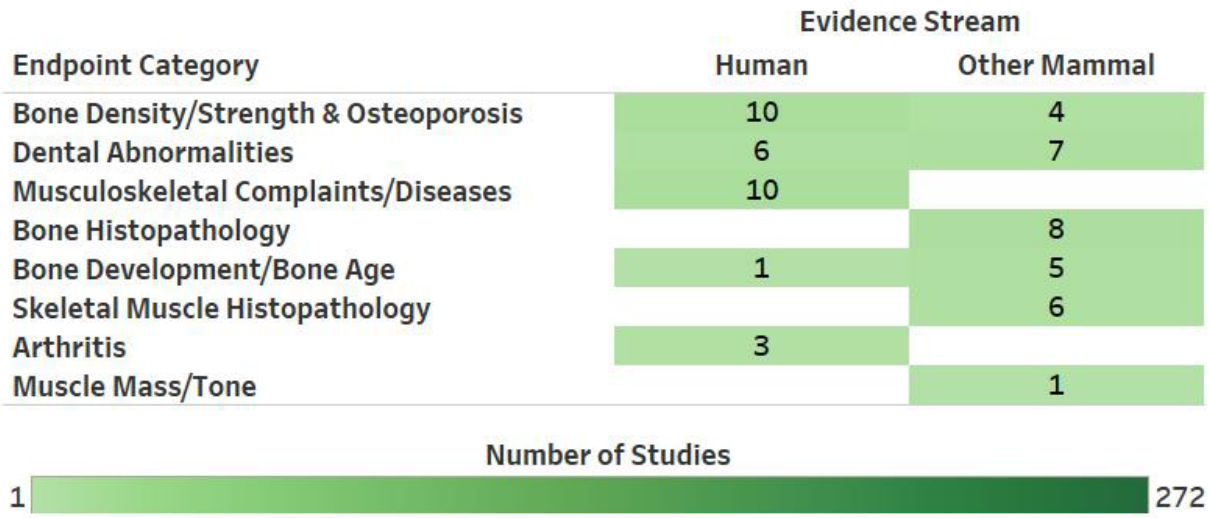


**Figure 20. Overview of Human and Other Mammalian Musculoskeletal Studies**

Summary of the database of studies evaluating exposures to PCB mixtures and musculoskeletal endpoints organized by endpoint category. Lists of studies included in each count can be accessed via the online interactive version of this figure (https://hawc.epa.gov/summary/visual/assessment/100500282/OverviewAllStudies/). Shading intensity corresponds with the number of studies in each category, from 1 to 272, which is the maximum number of nonhuman mammalian studies in any health endpoint category. The intent is to highlight not only differences in the distribution of studies across musculoskeletal endpoint categories but also to emphasize the number of musculoskeletal studies relative to the number of studies for other organs/systems.

Most human studies of bone density and strength were conducted among populations in which the major source of exposure to PCBs was through regular consumption of fish or marine mammals (see Figure 5). Five studies were from Sweden, where fatty fish from the Baltic Sea is a major source of PCB exposure (Rignell-Hydbom et al., 2009b; Hodgson et al., 2008; Weiss et al., 2006; Wallin et al., 2005; Glynn et al., 2000). In addition, studies have been conducted in aboriginal populations from Canada (Paunescu et al., 2013b; Paunescu et al., 2013a) and Greenland (Côté et al., 2006) where fish and marine mammals are major sources of PCB exposure in traditional diets. Because regular fish and marine mammal consumption can contribute both harmful and beneficial coexposures, generalizing these results to populations with other dietary patterns can be difficult (see Section 3.2.1). Of the studies referenced above, only two (Paunescu et al., 2013b; Paunescu et al., 2013a) included adjustments for possible harmful (e.g., mercury) and beneficial (e.g., omega 3 polyunsaturated fatty acids) coexposures from fish and marine mammals.

Several quantitative measures of bone health have been used in human and mammalian studies of PCB exposure. The stiffness index (SI) was used in two human studies of Canadian aboriginal populations (Paunescu et al., 2013b; Paunescu et al., 2013a), while most human studies evaluated bone mineral density (Fukushi et al., 2016; Cho et al., 2011; Rignell-Hydbom et al., 2009b; Hodgson et al., 2008; Weiss et al., 2006; Wallin et al., 2005; Glynn et al., 2000). One study measured both SI and density using quantitative ultrasound parameters (Côté et al., 2006). Bone mineral

density was also quantified in studies of rats perinatally exposed to PCBs (Elabbas et al., 2011; Cocchi et al., 2009). Other measurements evaluated in these rat studies included bone geometry (e.g., cortical thickness, bone length, total area), epiphyseal cartilage width, bone mineral content, and a range of biomechanical properties (e.g., bone strength as indicated by parameters of force, energy absorption, and stiffness). In studies of rats exposed to PCBs as adults, endpoints evaluated included tibia weight and femur morphometry (Andrews, 1989; Carter and Koo, 1984).

Dental abnormalities, including enamel defects, dental caries, and the occurrence of natal and neonatal teeth, have been examined in human studies of infants and children, with most studies using PCB levels in breast milk, blood, or serum to characterize exposure (Jan and Reinert, 2008; Jan et al., 2007; Wang et al., 2003; Alaluusua et al., 2002; Yakushiji et al., 1984). Early childhood caries can begin soon after tooth eruption and can have a lasting detrimental impact on dentition (e.g., higher risk of new carious lesions in both the primary and permanent teeth, enamel defects) and an increased risk of hospitalizations and emergency room visits, lost school days (leading to diminished ability to learn), and other markers of oral health-related quality of life (AAPD, 2020). Five studies in the database examined enamel defects and dental caries together with PCB exposure (Jan and Reinert, 2008; Laisi et al., 2008; Jan et al., 2007; Wang et al., 2003; Yakushiji et al., 1984). Four of these were conducted among populations with potential for higher PCB exposure via marine mammals and fish in the diet (Jan and Reinert, 2008), regional contamination from a manufacturing facility (Jan et al., 2007), maternal occupation (Yakushiji et al., 1984), and exposure via contaminated rice oil (Yu-Cheng population) (Wang et al., 2003); one was conducted among a general population sample in Finland (Laisi et al., 2008). Finally, three studies evaluated PCB exposure and the occurrence of natal and neonatal teeth (Jan et al., 2007; Wang et al., 2003; Alaluusua et al., 2002). Dental abnormalities have also been evaluated in rats, mice, and monkeys (see Figure 20); the primary endpoint assessed was tooth eruption, which is analogous to the occurrence of natal and neonatal teeth in humans (Sugawara et al., 2008; Sugawara et al., 2006; Branchi et al., 2002; Gerstenberger and Tripoli, 2001; Arnold et al., 1999; Arnold et al., 1995).

PCB exposure and arthritis have been evaluated in three human studies (see Figure 20), but each used a different definition of arthritis. One study considered all arthritis and arthritis subtypes, including rheumatoid arthritis, osteoarthritis, and unspecified arthritis, using data from the NHANES (Lee et al., 2007c). In a mortality study of PCB-exposed capacitor manufacturing workers, spondylitis arthritis was included as a noncancer cause of death (Mallin et al., 2004). In addition, a Japanese study measured blood levels of PCBs and gout (Nakamoto et al., 2013). Due to the limited number of studies available and the different etiologies of different arthritis types, further investigation would be needed to support an assessment of arthritis as a potential health effect of PCB exposure.

Overall, a limited number of epidemiological studies examined PCB exposure and musculoskeletal endpoints. Bone density and dental abnormalities were the most studied endpoints in humans, and together with available data from nonhuman mammalian studies, the

available information might be sufficient to support an evaluation of potential musculoskeletal hazards of PCB exposure, especially at higher exposure levels relative to the general population.

### 3.3.11. Nervous System

The nervous system is composed of the central nervous system (CNS), which includes the brain and spinal cord and the peripheral nervous system (PNS), which includes the ganglia and nerves outside the CNS. The CNS is the command center for a complex network of neurological functions. In humans, higher-order brain functions involved in cognitive processes are managed in the cerebral cortex, the gray matter on the outermost layer of the cerebrum. Specific regions in the left and right hemispheres of the cerebral cortex, which are further divided into the frontal, parietal, temporal, and occipital lobes, control a diverse set of functions, including language, movement, memory, vision, and executive functions (Mai and Paxinos, 2012). The PNS primarily serves as a conduit to connect the CNS to the periphery and other organs. The somatic (i.e., voluntary movement), autonomic (i.e., involuntary sympathetic and parasympathetic functions), and enteric (e.g., involuntary gastrointestinal control) nervous systems comprise the PNS. Signals from the CNS to the periphery are relayed via motor nerves and, conversely, sensory nerves provide feedback to the brain from the periphery.

The vulnerability of the brain to injury is well recognized and can manifest in a range of impairments depending on the timing and location(s) of injury. The primary mode of evaluating neurocognitive function in humans is neuropsychological assessment. Neuropsychological assessment typically includes a battery of performance-based tests across a variety of domains (e.g., cognition or intelligence, memory, and learning), which can be administered by a trained psychometrician or computer administered, in a controlled setting. Assessment can also include behavioral rating scales, which are used to assess behavior problems quantitatively such as externalizing behaviors (e.g., aggression, hyperactivity), internalizing behaviors (e.g., anxiety, depression), and social behavior (e.g., social skills, peer problems). These behavioral scales can be completed in a variety of settings by a clinician, parent, caregiver, or teacher or via self-assessment. When impairment measured across a set of specified criteria rises to a certain threshold, an individual might be diagnosed by a clinician with a brain-related disorder, such as a neurodevelopmental disorder (e.g., attention deficit hyperactivity disorder [ADHD] or autism spectrum disorder [ASD]), or a neurodegenerative disorder (e.g., Alzheimer's or Parkinson's disease). These disorders are characterized in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) (APA, 2013). However, it should be noted that decrements in neuropsychological function can result in considerable functional consequences even in the absence of a clinically diagnosed disorder (Sagiv et al., 2015; Rose, 1985).

An ever-growing literature evaluates exposures to neurotoxic chemicals in relation to poorer cognitive and behavioral function in humans across the lifespan. Many chemicals readily cross the placenta and can be transferred to infants via breast milk; thus, potential for exposure starts in early gestation, when the neural tube is first forming, and continues throughout pregnancy

as brain cells proliferate, differentiate, and migrate (Goasdoué et al., 2017; Barone et al., 2000; Rice and Barone, 2000). This heightened vulnerability to neurotoxic chemical exposure continues during synaptogenesis and myelination, processes that persist in some brain regions through early adulthood. Among older adults, exposure to neurotoxicants can accelerate declines in cognitive function at the subclinical level (Weiss, 2010), placing elderly individuals at potentially greater risk of developing clinically relevant neurodegenerative disorders (e.g., Alzheimer's disease, Parkinson's disease) (Siblerud et al., 2019; Monnet-Tschudi et al., 2006).

Of the epidemiological studies that met inclusion criteria, 214 evaluated PCB exposures and neuropsychological endpoints in human adults and children (see Figure 4). Below we summarize those studies evaluating PCB exposures with the following seven domains: (1) cognitive function; (2) attention, impulse control, externalizing behaviors, and internalizing behaviors (including activity level); (3) executive function; (4) social cognition and social behavior, including traits related to ASDs; (5) motor function/development; (6) brain aging disorders; and (7) auditory function (see Figure 21). That endpoints described in each domain are not mutually exclusive should be noted, as they arise in an interconnected brain. For example, executive function bears greatly on cognitive processes involved in planning and working memory and is often impaired among individuals with ADHD and ASD. Additional endpoint categories identified in eligible studies outside these domains include olfactory function, visual function, neurological condition, peripheral sensation or pain, headache, dizziness, fatigue/level of consciousness, sleep problems, neurological disease mortality, neurophysiology or neuroimaging, and play behavior (see Figure 21). However, these endpoint categories are less informative for hazard identification because they are broadly defined (e.g., neurological condition), provide a limited database (e.g., olfactory function, sleep problems, play behavior), or are inherently subjective (e.g., headache, fatigue). In addition, endpoints within the neurophysiology/neuroimaging category (e.g., sensory and motor nerve conduction, nerve conduction velocity, event-related potentials, neuroimaging) might be most useful to inform possible mechanisms/modes of action once specific apical nervous system effects have been implicated. As such, this review of the human data for neurological endpoints has focused on the aforementioned seven domains.

| Endpoint Category | Evidence Stream: Human | Evidence Stream: Other Mammal |
|---|---|---|
| Attention, Impulse Control, & Externalizing/Internalizing Behaviors | 63 | 70 |
| Cognitive Function | 84 | 42 |
| Motor Function/Development | 65 | 42 |
| Brain Weight & Histopathology | | 69 |
| Executive Function | 20 | 21 |
| Social Cognition & Social Behavior | 16 | 15 |
| Auditory Function | 12 | 15 |
| Neurophysiology/Neuroimaging | 14 | 9 |
| Neurotransmitter Levels | | 21 |
| Neurological Condition | 19 | |
| Peripheral Sensation/Pain | 15 | 2 |
| Level of Consciousness/Fatigue | 8 | 7 |
| Brain Aging Disorders | 13 | |
| Visual Function | 11 | 1 |
| Neurological Disease Mortality | 10 | |
| Headache | 9 | |
| Dizziness | 5 | |
| Olfactory Function | 2 | 1 |
| Play Behavior | 3 | |
| Sleep Problems | 3 | |
| "Behavioral Function" | | 1 |


**Figure 21. Overview of Human and Other Mammalian Nervous System Studies**

Summary of the database of studies evaluating exposures to PCB mixtures and nervous system endpoints organized by endpoint category. Lists of studies included in each count can be accessed via the online interactive version of this figure (https://hawc.epa.gov/summary/visual/assessment/100500282/OverviewAllStudies/). Shading intensity corresponds with the number of studies in each category, from 1 to 272, which is the maximum number of nonhuman mammalian studies in any health endpoint category. The intent is to highlight not only differences in the distribution of studies across nervous system endpoint categories but also to emphasize the number of nervous system studies relative to the number of studies for other organs/systems.

Additionally, a database of studies is summarized that examined PCB exposures and nonhuman mammalian behaviors that have face validity to the behavioral domains examined in the human literature. We identified 174 published studies in mammals other than humans that evaluated nervous system endpoints applicable to human neurobehavioral domains (see Figure 4), including studies that examined endpoints such as neuropathology and neurochemistry (see Figure 21). Most nervous system studies in nonhuman mammals were conducted using rat models (see Figure 8). Endpoints have also been studied in mice, nonhuman primates, and other species. In

most studies, PCBs were administered orally (e.g., in the diet or via oral gavage) (see Figure 9). Fewer studies administered PCBs via alternative routes of exposure, including inhalation and injection (e.g., intraperitoneal or subcutaneous). As described above, the nervous system is especially sensitive to effects of chemical exposure from the gestational period through early adulthood, and such exposure could result in permanent disruption (Barone et al., 2000). Thus, for assessing potential hazard to the nervous system, it is important for a database to include studies of exposures during this window. In the PCB database, gestational and lactational exposures were investigated most often, with about half of these studies including evaluations of endpoints in the adult offspring (see Figure 22). Fewer studies examined developmental PCB exposures administered directly to juvenile animals or nervous system endpoints following adult exposures to PCBs.

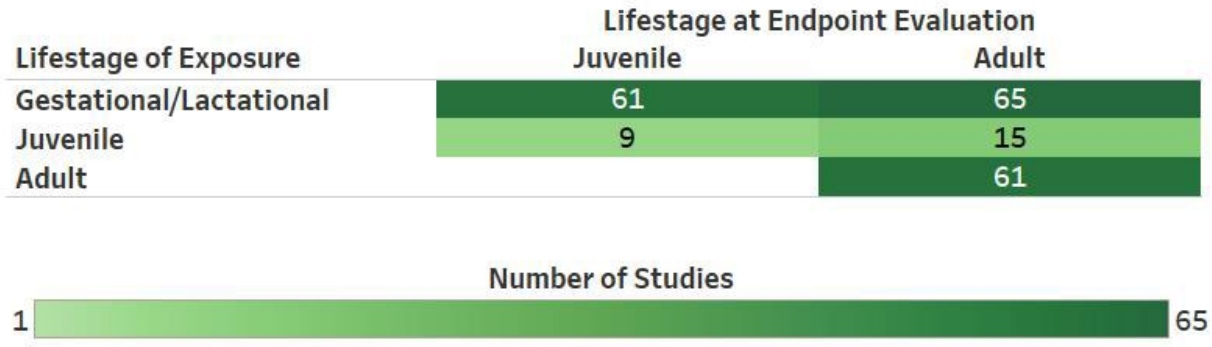


**Figure 22. Overview of Nonhuman Mammalian Studies of Nervous System Endpoints by Lifestage of Exposure and Lifestage at Endpoint Evaluation**

Summary of the database of studies in nonhuman mammals evaluating exposures to PCB mixtures and nervous system endpoints organized by life stage of exposure and life stage at endpoint evaluation. Lists of studies included in each count can be accessed via the online interactive version of this figure (https://hawc.epa.gov/summary/visual/assessment/100500282/NervousSystemEndpointsNonhumanMammals/), which can be filtered by endpoint category (options: activity levels, affective behavior, attention, auditory function, brain weight & histopathology, cognitive function, executive function, inhibitory control, level of consciousness, motor function/development, neurophysiology/neuroimaging, neurotransmitter levels, olfactory function, peripheral sensation/pain, social behavior/development, visual function), exposure route (options: inhalation, injection, oral), and species (options: guinea pig, mink, mouse, nonhuman primate, rabbit, rat, sheep, swine). Shading intensity corresponds with the number of studies in each category, from 1 to 65, which is the maximum number of studies in any category.

Cognition comprises the mental processes involved in a variety of functions, such as reasoning, learning, memory, and problem solving. Epidemiological studies examining PCB exposure typically assess cognition by measuring intellectual function using Intelligence Quotient (IQ) tests. In addition to generating a total IQ score, these tests can be grouped into verbal and nonverbal IQ and commonly include subscales of intelligence across more specific domains, such as working memory, processing speed, attention, and language comprehension. Some studies also

employ domain-specific tests that assess specific aspects of cognition, such as memory, learning, and visuospatial abilities. An advantage of domain-specific tests is that they can allow for better localization of potential damage to the brain than an omnibus IQ score (White et al., 2009).

Sixty-nine published studies examined developmental exposure to PCBs and cognitive function in children (some reporting results in multiple publications for the same study population) (see Figure 23). In most of these studies, primarily prospective cohort studies (see Figure 6), PCB exposure was measured in biological media during the prenatal period (e.g., umbilical cord serum/plasma, maternal serum/plasma collected during pregnancy) or in the early postnatal/childhood period (e.g., breast milk, serum/plasma collected in children) (see Figure 7). Many of these studies evaluated infant and toddler cognition using scales such as the Bayley Scales of Infant Development and the Fagan Test of Infant Intelligence [e.g., (Lynch et al., 2012; Park et al., 2010; Wilhelm et al., 2008b; Walkowiak et al., 2001; Darvill et al., 2000; Winneke et al., 1998; Koopman-Esseboom et al., 1996; Rogan and Gladen, 1991; Yu et al., 1991; Gladen et al., 1988)]. Using slightly different instruments, these studies all capture aspects of cognition during infancy/toddlerhood, allowing for potential hazard identification across numerous studies. However, results from studies of neuropsychological measures of infants and toddlers can be noisy due to difficulty in achieving a desired state for testing in younger children; results in older children are more reliable (Skovgaard et al., 2004). Several studies evaluated developmental PCB exposure and general intelligence scales in older, school-age children using tests such as the Wechsler Scale for Intelligence in Children and the McCarthy Scales of Children's Abilities [e.g., (Grandjean et al., 2012b; Zhou et al., 2011a; Zhou et al., 2011b; Stewart et al., 2008; Gray et al., 2005; Jacobson and Jacobson, 2002; Vreugdenhil et al., 2002; Jacobson and Jacobson, 1996; Chen et al., 1992; Yu et al., 1991)]. In addition to full-scale IQ, these tests often report domain-specific subscales that assess verbal and nonverbal intelligence, processing speed, and visuospatial skills. This large database of studies on IQ provides one of the best opportunities for assessing potential associations of PCB exposure with neurodevelopment. As mentioned above, however, a downside of these omnibus measures is that they might not capture effects on specific intellectual domains, such as working memory and visuospatial skills. Several of these studies and others did use domain-specific neuropsychological tests to assess specific cognitive skills, such as memory and learning, and academic performance (Wang et al., 2015; Orenstein et al., 2014; Grandjean et al., 2012b; Roze et al., 2009; Newman et al., 2006; Vreugdenhil et al., 2004a; Jacobson and Jacobson, 2003; Patandin et al., 1999; Jacobson et al., 1992; Jacobson et al., 1990). Only a few studies reported on developmental exposure to PCBs and academic achievement (Strøm et al., 2014; Gladen and Rogan, 1991), learning disabilities (Lee et al., 2007a), and intellectual disability (Hamra et al., 2019; Lyall et al., 2017). The smaller body of literature on these individual cognitive abilities might make hazard identification more difficult for these domain-specific functions.


**Figure 23. Overview of Human Studies of Nervous System Endpoints by Endpoint Category and Exposure Lifestage**

Summary of the database of human studies evaluating exposures to PCB mixtures and nervous system endpoints organized by endpoint category and life stage of exposure assessment. Lists of studies included in each count can be accessed via the online interactive version of this figure (https://hawc.epa.gov/summary/visual/assessment/100500282/NervousSystemEndpointsHumans/), which can be filtered by study design (options: case-control, cohort, cross-sectional, other), population (options: accidental, contaminated schools and other buildings, fish/marine mammal [diet], general population, occupational, residents in contaminated area, Yusho/Yu-Cheng), exposure metric (options: blood, breast milk, child blood, cord blood, dietary estimates, maternal blood, occupational/JEM, other metric [includes dust and modeled estimates], other tissue), and lifestage of endpoint evaluation (options: adolescent, adult, child, early childhood, infant, NR). Shading intensity corresponds with the number of studies in each category, from 1 to 69, which is the maximum number of studies in any category.

Fifteen published studies (some reporting results in multiple publications for the same cohort) assessed PCB exposure and cognitive function among adults (see Figure 23). Among these, most were cross-sectional, and the remaining study designs were retrospective cohort (Lin et al., 2010; Lin et al., 2008), prospective cohort (Tanner et al., 2020), and case-control (Kilburn et al., 1989). PCB exposure was measured primarily in biological media (e.g., serum/plasma/blood/tissue) collected concurrent with or after exposure. Several studies assessing cognition were conducted among occupationally exposed subjects, primarily related to production of electrical capacitors (Fimm et al., 2017; Seegal et al., 2013; Seegal, 2011; Kilburn et al., 1989; Fischbein et al., 1979), and among adults primarily exposed through consumption of

contaminated fish (Schantz et al., 2001) or rice oil (i.e., Yu-Cheng) (Lin et al., 2010; Lin et al., 2008). The studies most informative for hazard identification are those using reliable, validated test instruments of cognitive function, such as the Wechsler Adult Intelligence Scale (WAIS) and the Wechsler Memory Scale (WMS). Eight studies evaluated exposure to PCBs and cognition using the WAIS (Tanner et al., 2020; Przybyla et al., 2017; Bouchard et al., 2014; Seegal et al., 2013; Lin et al., 2010; Lin et al., 2008; Peper et al., 2005; Kilburn et al., 1989), and eight used the WMS (Tanner et al., 2020; Seegal et al., 2013; Haase et al., 2009; Fitzgerald et al., 2008; Lin et al., 2008; Peper et al., 2005; Schantz et al., 2001; Kilburn et al., 1989). In addition to the WAIS and WMS, the California Verbal Learning Test (CVLT), a well-known, validated test of verbal learning and memory that can also inform PCB hazard assessment among adults, was used in five studies (Tanner et al., 2020; Fimm et al., 2017; Seegal et al., 2013; Fitzgerald et al., 2008; Schantz et al., 2001).

Within the database are 42 nonhuman mammalian studies that evaluated cognitive function in a variety of species, including rodents and nonhuman primates (see Figure 21, Figure 8). Of these, most evaluated cognitive function in offspring exposed to PCBs during the gestational or lactational period (see Figure 24). Eleven studies investigated cognitive endpoints following direct PCB exposure in juvenile or adult mammals. Many cognitive tests measure spatial learning and memory; the most common of these assays include the Morris water maze (MWM), radial arm maze (RAM), spatial alternation (sometimes referred to as reversal learning), and novel object recognition assays (NOR; sometimes referred to as object-based attention). The MWM, RAM, and spatial alternation assays are well established in animal models (Wenk, 2004). NOR assays can additionally provide insight into attention and internalizing/externalizing behaviors (Vogel-Ciernia and Wood, 2014). Many of the included studies evaluated spatial learning and memory using these tests, including four studies in nonhuman primates (Rice, 1998; Schantz et al., 1989; Levin et al., 1988; Bowman et al., 1978)] and many others in rodents [e.g., (Nam et al., 2014; Elnar et al., 2012; Tian et al., 2011; Yang et al., 2009; Sugawara et al., 2006; Zahalka et al., 2001; Gilbert et al., 2000; Roegge et al., 2000; Corey et al., 1996; Lilienthal and Winneke, 1991)]. Other tests of cognitive function, learning, and memory include operant paradigms (e.g., nonspatial reversal learning, fixed interval, progressive ratio, differential reinforcement of low/high rate, attention set-shifting, Wisconsin card sorting task, passive/active avoidance). Operant paradigms are considered robust for testing learning and memory in animals and have face validity to cognitive responses in humans. The database contains many studies that used operant-based tests in mammals, including seven studies in nonhuman primates (Rice and Hayward, 1999; Rice, 1998, 1997; Rice and Hayward, 1997; Schantz et al., 1989; Mele et al., 1986; Bowman et al., 1978) and others in rats [e.g., (Monaikul et al., 2017; Meyer et al., 2015; Sable et al., 2006; Widholm et al., 2004; Bushnell et al., 2002; Berger et al., 2001; Geller et al., 2001; Widholm et al., 2001; Nishida et al., 1997; Lilienthal et al., 1990)].

| Endpoint Category | | Evidence Stream: Other Mammal | Lifestage of Exposure: Gestational/Lactational | Juvenile | Adult |
|---|---|---|---|---|---|
| Attention, Impulse Control, & Externalizing/Internalizing Behaviors | Activity Levels | 38 | 23 | 1 | 14 |
| | Affective Behavior | 39 | 29 | 2 | 8 |
| | Attention | 4 | 4 | | |
| | Inhibitory Control | 23 | 16 | 7 | |
| Brain Weight & Histopathology | | 69 | 35 | 7 | 36 |
| Cognitive Function | | 42 | 31 | 7 | 4 |
| Motor Function/Development | | 42 | 29 | 1 | 13 |
| Executive Function | | 21 | 14 | 7 | |
| Neurotransmitter Levels | | 21 | 5 | 3 | 14 |
| Auditory Function | | 15 | 15 | | |
| Social Cognition & Social Behavior | | 15 | 12 | 1 | 4 |
| Neurophysiology/Neuroimaging | | 9 | 8 | | 1 |
| Level of Consciousness/Fatigue | | 7 | 2 | 3 | 4 |
| Peripheral Sensation/Pain | | 2 | 1 | | 1 |
| "Behavioral Function" | | 1 | | | 1 |
| Olfactory Function | | 1 | 1 | | |
| Visual Function | | 1 | 1 | | |

Number of Studies

1 69

**Figure 24. Overview of Nonhuman Mammalian Studies of Nervous System Endpoints by Endpoint Category and Lifestage of Exposure**

Summary of the database of studies in nonhuman mammals evaluating exposures to PCB mixtures and nervous system endpoints organized by endpoint category and lifestage of exposure. Lists of studies included in each count can be accessed via the online interactive version of this figure (https://hawc.epa.gov/summary/visual/assessment/100500282/NervousSystemEndpointsNonhumanMammals/), which can be filtered by exposure route (options: inhalation, injection, oral), species (options: guinea pig, mink, mouse, nonhuman primate, rabbit, rat, sheep, swine), lifestage at endpoint evaluation (options: adult, juvenile), and lifestage of exposure (options: adult, gestational/lactational, juvenile). Shading intensity corresponds with the number of studies in each category, from 1 to 69, which is the maximum number of studies in any category.

Another category of endpoints captures behaviors related to ADHD, including attention and externalizing behaviors such as impulsivity/hyperactivity; other externalizing behaviors, such as aggression and disruptive behaviors that, at the extreme, are characteristic to disorders such as conduct disorder and internalizing behaviors such as anxiety and depression. Evaluating many of these behaviors in children involves using behavioral rating scales completed by the parent or the teacher. Behaviors rated include inattention, impulsivity/hyperactivity and other externalizing behaviors, and internalizing behaviors like anxiety. A limitation of these behavioral rating scales is that they are subjective and introduce risk for informant bias (Emser et al., 2018; Edwards et al., 2007). However, they are valuable for assessing child behavior problems across different environments and can provide information for assessing PCB exposures and problem behaviors such as inattention, hyperactivity/impulsivity, and internalizing behaviors. Performance-based tests, used to measure sustained attention and response inhibition, are conducted with reaction time tests or continuous performance tests. For these assessments, which are typically computer based, the individual must attend to a continuous activity or stimulus, respond to target stimuli, and inhibit response to nontarget stimuli. These tests have the advantage of being a more objective measure of behavior than behavioral rating scales but offer only a snapshot of behavior at a single time point in a single environment and therefore do not reflect behavior across different settings (e.g., home, school).

PCB exposures during the prenatal/early postnatal periods and endpoints associated with attention, impulse control, and externalizing/internalizing behaviors were evaluated in 43 studies (see Figure 23). Many of these studies assessed attention and response inhibition with performance-based tests [e.g., (Neugebauer et al., 2015; Boucher et al., 2012a; Forns et al., 2012; Grandjean et al., 2012b; Roze et al., 2009; Stewart et al., 2006; Stewart et al., 2005; Vermeir et al., 2005; Jacobson and Jacobson, 2003; Jacobson et al., 1992)]. Although the type of test varied, most produce measures of reaction time, reaction time variability, errors of omission, and errors of commission, which are markers of attention and response inhibition. Thus, this large number of studies provides an opportunity to evaluate potential PCB exposure hazard for these functions. Many studies also investigated developmental PCB exposure and behavioral rating scales [e.g., (Forns et al., 2016; Kyriklaki et al., 2016; Zhang et al., 2016; Wang et al., 2015; Newman et al., 2014; Boucher et al., 2012b; Tatsuta et al., 2012; Sagiv et al., 2010; Roze et al., 2009; Chen et al., 1994)]. Only three studies investigated developmental exposure to PCBs and parent reports of ADHD diagnosis or stimulant medication use (Lenters et al., 2019; Strøm et al., 2014; Lee et al., 2007a). Thus, few data are available for assessing potential associations of developmental PCB exposure with clinically diagnosed ADHD, but a greater database enables the evaluation of potential effects on quantitative traits related to ADHD.

Twenty studies evaluated PCB exposure and attention and externalizing/internalizing behaviors among adults (see Figure 23). Among this group of studies, most were cross-sectional, seven were cohort in design, and one was a case-control study. PCB exposure was based on

measurements in biological media in all studies (e.g., serum, plasma, blood, tissue). Seven studies in adults evaluated exposure to PCBs and the WAIS digit symbol substitution/coding test, a reliable measure of attention that is informative for assessing potential PCB hazard (Tanner et al., 2020; Przybyla et al., 2017; Bouchard et al., 2014; Fitzgerald et al., 2008; Lin et al., 2008; Peper et al., 2005; Schantz et al., 2001). Several studies assessing internalizing behaviors were conducted among occupationally exposed subjects (see Figure 23), primarily related to production of electrical capacitors (Gaum et al., 2019; Fimm et al., 2017; Gaum et al., 2017; Esser et al., 2015; Esser et al., 2014; Gaum et al., 2014; Seegal et al., 2013; Kilburn et al., 1989; Fischbein et al., 1979) or among adults exposed to PCBs through the air (Peper et al., 2005) or diet (Schantz et al., 2001). Most studies examining PCB exposure and internalizing behaviors (e.g., depression, anger, and anxiety) used validated self-report symptom questionnaires, such as the Beck Depression Inventory (BDI) (Tanner et al., 2020; Gaum et al., 2017; Seegal et al., 2013; Fitzgerald et al., 2008), State-Trait Anxiety Inventory (STAI) (Tanner et al., 2020; Seegal et al., 2013; Fitzgerald et al., 2008), Geriatric Depression Scale (GDS) (Lin et al., 2008), EQ-5D-3L (Esser et al., 2015; Esser et al., 2014), Symptom Checklist-90-Revised (SCL-90-R) (Santiago-Rivera et al., 2007), Center for Epidemiologic Studies Depression Scale (CES-D) (Santiago-Rivera et al., 2007), and Patient Health Questionnaire (PHQ-D) (Gaum et al., 2019; Gaum et al., 2014).

In animals, information about attention can be derived from cognitive function tasks, including object-based attention tasks such as NOR. In these tests, a reduction in time interacting with an object can be interpreted as a deficit in attention. These assays also overlap with other aspects of cognitive function, such as short-term visual memory. Four nonhuman mammalian studies in the database specifically evaluated PCB exposures and NOR or object-based attention (see Figure 24).

As in humans, impulsivity and inhibitory control can be measured in animals using several operant behavioral paradigms, such as differential reinforcement of low-rate, fixed-interval, progressive-ratio, fixed-ratio, and reversal tasks (Mitchell, 2014; Barrett and Vanover, 2004; Arnold et al., 2003). These assays — considered "gold standard" tests of impulsivity and attention — can detect subtle shifts in inhibitory control in the form of perseverative errors, and other output metrics can additionally be used to evaluate learning, working memory, and cognitive flexibility over time. Twenty-three studies in the database measured inhibitory control using operant or object-based attention assays in nonhuman primate or rodent models (see Figure 24). Sixteen studies evaluated these endpoints in nonhuman mammals exposed through gestation or lactation, while seven studies evaluated direct PCB exposures to juvenile mammals, including four studies in nonhuman primates that evaluated direct exposure during the preweaning period (Rice and Hayward, 1999; Rice, 1998, 1997; Rice and Hayward, 1997).

Hyperactivity is considered a type of externalizing behavior and can be measured directly by measuring the distance traveled by rodents in spontaneous locomotor and open field assays, which are common "gold standard" behavioral paradigms (Pierce and Kalivas, 2007). Indirect

measures of hyperactivity include measurement of movement in tests designed to assess other behavioral domains (e.g., MWM), although such activity measurements relate more to general motor function and have minimal validity for evaluating externalizing behavior. Thirty-eight studies provided data on general activity levels with PCB exposure, including spontaneous locomotor activity, open field, and activity levels in other assays using nonhuman primates, rats, and mice (see Figure 24). Most studies evaluated developmental PCB exposure via the dam while the remaining studies assessed direct juvenile or adult exposure. Although a relatively large number of studies measured PCB exposure and activity levels, further scrutiny of study methods and endpoint reporting would be needed to identify those most valid for evaluating externalizing/internalizing behaviors.

Open field and spontaneous locomotor behavior assays are well-established methods that can provide insight into emotional state and affect in rodents as they tend to avoid open spaces. Thus, assessing where in the arena animals travel (along the edges vs. in the center) can provide insight into shifts in an animal's behavior toward risk-taking or risk-aversive (i.e., anxiety-like) emotional states. The elevated plus maze (EPM) and elevated zero maze (EZM) are also used to determine emotional reactivity and risk-taking behavior in rodents (Braun et al., 2011; File et al., 2004). Thirty-nine studies tested affective behavior with PCB exposure (see Figure 24). Many rodent studies used "gold standard" assays, including the open field test, usually following developmental PCB exposure via the dam [e.g., (Nam et al., 2014; Elnar et al., 2012; Tian et al., 2011; Sugawara et al., 2006; Meerts et al., 2004b; Branchi et al., 2002; Lilienthal et al., 1990; Pantaleoni et al., 1988; Storm et al., 1981)], but also in one study of male rats exposed during adolescence (Casey et al., 1999) and in four studies evaluating adult exposure (Bavithra et al., 2017; Sumathi et al., 2016; Selvakumar et al., 2013; Freeman et al., 2000). Other studies tested performance in a spontaneous locomotor behavior assay in rodents or nonhuman primates, with six studies evaluating developmental exposure via the dam (Colciago et al., 2009; Steinberg et al., 2007; Goldey and Crofton, 1998; Bowman and Heironimus, 1981; Bowman et al., 1981; Bowman et al., 1978) and one study evaluating adult exposure (Freeman et al., 2000). Eight studies evaluated rodents in the EPM or EZM, seven evaluating developmental exposure via the dam (Gillette et al., 2017; Bell et al., 2016; Nam et al., 2014; Elnar et al., 2012; Curran et al., 2011a; Tian et al., 2011; Colciago et al., 2009), and one study evaluating adult exposure (Bavithra et al., 2017).

Executive function is a multidimensional construct involved in higher-order cognitive and behavioral processes; it is critical for planning, problem solving, sustaining attention, and inhibitory control. These functions underlie goal-oriented behavior and emotional regulation, and can have important implications for academic achievement, social behavior, risk-taking behavior, and socioeconomic attainment. Features of executive function that have been covered in other endpoint categories are not included below. For example, sustained attention and response inhibition (measured with continuous performance tests), both of which are core features of executive function, were included under the attention, externalizing behaviors, and internalizing behaviors

category and are not described here. In addition, some tests of working memory, another seminal feature of executive function, were included under cognitive function (e.g., Working Memory subtest of the Wechsler Scale for Intelligence in Children).

Eight human studies evaluated PCB exposures during the prenatal/early postnatal periods and measures of executive function (not included in other endpoint categories) (see Figure 23). These include skills around planning and organization [e.g., (Rocha-Amador et al., 2009; Vreugdenhil et al., 2004a)], cognitive flexibility [e.g., (Jacobson and Jacobson, 2003)], and working memory [e.g., (Jacobson and Jacobson, 2003; Jacobson et al., 1992)]. Twelve studies evaluated PCB levels measured in biological (e.g., serum, plasma, blood, tissue) or environmental media during adulthood and measures of executive function (not included in other endpoint categories) (see Figure 23). Among these 12 studies, most were cross-sectional, 2 were retrospective cohort (Lin et al., 2010; Lin et al., 2008), 1 was prospective cohort (Tanner et al., 2020), and 1 was case-control (Kilburn et al., 1989). Several studies in adults evaluated exposure to PCBs and tests of executive function that are informative for assessing potential PCB hazard, including the Wisconsin Card Sorting Test (Tanner et al., 2020; Seegal et al., 2013; Haase et al., 2009; Fitzgerald et al., 2008; Schantz et al., 2001), the Trail Making Test (Tanner et al., 2020; Fimm et al., 2017; Seegal et al., 2013; Haase et al., 2009; Fitzgerald et al., 2008; Peper et al., 2005; Schantz et al., 2001; Kilburn et al., 1989), the Stroop Color and Word Test (Tanner et al., 2020; Seegal et al., 2013; Haase et al., 2009; Fitzgerald et al., 2008; Schantz et al., 2001), and the Short Category Test (Schantz et al., 2001). Overall, several well-designed studies administered reliable tests of executive function in developmental and adult populations that should provide sufficient evidence for potential hazard identification of PCBs and executive function.

Nonhuman mammalian studies that examined PCBs and executive function used delayed spatial alternation (DSA), reversal learning/alternation (e.g., operant-based tasks, Y-maze, T-maze), and attention set-shifting (e.g., Wisconsin card sorting test in nonhuman primates, cued operant tests in rodents). Such assays can detect subtle shifts in executive function domains commonly perturbed in human neurodevelopmental disorders, such as ASD and ADHD. Twenty-one studies reported evaluations of executive function (see Figure 21), including 9 that investigated DSA, reversal learning, or attention set-shifting in nonhuman primates (Rice, 1998; Rice and Hayward, 1997; Schantz et al., 1989; Levin et al., 1988; Bowman et al., 1978) and rats (Meyer et al., 2015; Widholm et al., 2004; Widholm et al., 2001; Zahalka et al., 2001) and 14 that evaluated executive function through operant-based tasks in nonhuman primates (Rice and Hayward, 1999; Rice, 1997; Mele et al., 1986) and rats (Miller et al., 2017b; Monaikul et al., 2017; Lombardo et al., 2015; Meyer et al., 2015; Sable et al., 2006; Widholm et al., 2004; Bushnell et al., 2002; Taylor et al., 2002; Berger et al., 2001; Geller et al., 2001; Lilienthal et al., 1990). Of these executive function studies (see Figure 24), 14 were conducted using developmental exposures via the dam, and 7 evaluated direct exposure to young animals, including 4 that administered PCBs directly to neonatal nonhuman primates (Rice and Hayward, 1999; Rice, 1998, 1997; Rice and Hayward, 1997) and 3 that

evaluated exposure to adolescent rats (Monaikul et al., 2017; Lombardo et al., 2015; Berger et al., 2001). The administered tests are considered "gold standard" and have suitable face validity to the abovementioned tests that assess human executive function.

ASD is characterized by restricted interests and behaviors, including stereotyped patterns of behavior, sensory sensitivities, and circumscribed interests. Social cognition, which is often impaired among individuals with ASD, involves the ability to interpret and respond to social cues, communication, and interaction. These traits (or behaviors) can be measured on a continuum in the general population using tests such as the Social Responsiveness Scale (SRS); scores exhibit a fairly normal distribution with those at the extreme impaired end indicating higher risk for ASD (Constantino, 2011). Deficits in social cognition have been associated with lifelong educational, vocational, adaptive functioning, and mental health challenges among individuals with and without a clinically diagnosed disorder. Social behavior and traits related to ASD can be measured using behavioral rating scales, observation, and performance-based tests, such as tests of theory of mind.

Fourteen human studies evaluated PCB exposure during the prenatal/early postnatal periods and social behavior and other traits related to ASD (see Figure 23). These include seven studies of clinically diagnosed ASD (Bach et al., 2020; Granillo et al., 2019; Hamra et al., 2019; Brown et al., 2018; Lyall et al., 2017; Cheslack-Postava et al., 2013; Otake et al., 2006) and seven studies of quantitative traits related to ASD, assessed using behavior rating scales (Alampi et al., 2021; Bernardo et al., 2019; Kim et al., 2018; Nowack et al., 2015; Braun et al., 2014; Doi et al., 2013; Plusquellec et al., 2010). Two studies assessed PCB exposure and social behavior and other traits related to ASD among adults. One was an occupational study evaluating two measures of social behavior, the Freiburg Personality (FPI-R) and aggregated secondary factors (introversion, low sociability) (Peper et al., 2005). The other included individuals stated to have ASD in a postmortem brain study (Mitchell et al., 2012); however, no information was reported for how ASD was determined. The few studies on PCBs and social behavior and the diversity in assessment methods could make hazard identification challenging.

Nonhuman mammalian studies could supplement the small human database but modeling social cognition and social behavior in animals presents unique challenges in that many aspects of human social interaction are not recapitulated in other species, especially rodent species (Yang et al., 2011). However, researchers can take advantage of species-specific social interactions to assess animal social behaviors that have face validity to aspects of human social behaviors, such as social approach/social novelty assays (Mathiasen and Dicamillo, 2010; Winslow, 2003), social-conditioned place preference (SCPP) (Pearson et al., 2012), and maternal behavior (Lucion and Bortolini, 2014). In addition, some aspects of reproductive behaviors rely on social cognition and can be assessed in rodents by measuring ultrasonic vocalizations (USVs) between opposite-sex conspecifics (Barfield et al., 1979) or through paced mating tests (Zipse et al., 2000).

Fifteen studies in the database evaluated PCB exposures and social behavior in rodents (see Figure 21). Of these, five studies evaluated social approach/social novelty (Reilly et al., 2018;

Karkaba et al., 2017; Bell et al., 2016; Reilly et al., 2015; Fanini et al., 1990), five measured USVs in social or sociosexual contexts (Krishnan et al., 2019; Topper et al., 2019; Krishnan et al., 2018; Bell et al., 2016; Steinberg et al., 2007), four evaluated paced mating behavior (Krishnan et al., 2018; Steinberg et al., 2007; Chung et al., 2001; Chung and Clemens, 1999), three investigated maternal behavior (Krishnan et al., 2019; Elnar et al., 2012; Brezner et al., 1984), and two studies assessed mate preference (Hernandez Scudder et al., 2021; Hernandez Scudder et al., 2020). With the exception of four studies conducted following adult exposure and one study assessing juvenile exposure, most studies of social behavior evaluated offspring following developmental exposure via the dam (through prenatal or lactational exposure) (see Figure 24). Although relatively few nonhuman mammalian studies examined PCB exposures and specific aspects of social behavior, the existing studies were well conducted and can supplement human study observations, especially in assessments of the potential effect(s) of developmental PCB exposure on social behavior.

Forty-seven studies in humans evaluated PCB exposures during the prenatal/early postnatal periods and motor function (see Figure 23). Of these, most assessed motor function of infants or toddlers, primarily using the Bayley Scales of Infant Development, Psychomotor Development Index (PDI) [e.g., (Ruel et al., 2019; Kim et al., 2018; Brucker-Davis et al., 2015; Gascon et al., 2013; Park et al., 2009; Wilhelm et al., 2008a; Daniels et al., 2003; Walkowiak et al., 2001; Koopman-Esseboom et al., 1996; Rogan and Gladen, 1991)]. Only 13 studies of PCBs examined gross/fine motor function in older children (Boucher et al., 2016; Høyer et al., 2015; Šovčíková et al., 2015; Wang et al., 2015; Grandjean et al., 2012b; White et al., 2011; Plusquellec et al., 2010; Roze et al., 2009; Vermeir et al., 2005; Winneke et al., 2005; Vreugdenhil et al., 2004a; Jacobson and Jacobson, 2003; Vreugdenhil et al., 2002). Overall, more data are available to inform hazard assessment for motor endpoints in infants and toddlers, although there are caveats of measuring these functions in early childhood, as noted earlier3.3.11. The few studies and lack of diversity in tests of these functions could make hazard identification challenging for fine/gross motor function in older children.

Eighteen studies evaluated PCB levels in biological (e.g., serum, plasma, blood, tissue) or environmental media during adulthood and endpoints associated with motor function (see Figure 23). Among these, eleven were cross-sectional, six were cohort studies, and one was case-control. Among these 18 studies, 8 used reliable instruments that would be most informative for assessing potential hazard, such as the Grooved Pegboard Test, Finger Tapping Test, Static Motor Steadiness Test, and Motor Performance Series (Gaum et al., 2021; Tanner et al., 2020; Fimm et al., 2017; Seegal et al., 2013; Haase et al., 2009; Fitzgerald et al., 2008; Lin et al., 2008; Kilburn et al., 1989). All but one of these studies (Kilburn et al., 1989) were conducted in samples with more than 100 participants.

Tests for motor activity and coordination are one of the most common types of assays performed in animal models of developmental neurotoxicity. Tests that measure motor function directly in juvenile or adult animals include spontaneous locomotor activity, open field, rotarod,

beam walking, and gait analysis (Pierce and Kalivas, 2007; Carter et al., 2001). Aspects of motor activity can also be derived from other assays that track the animal's motion automatically (e.g., tests that use mazes or multichambered arenas). Spontaneous locomotor activity and open field assays are considered "gold standard" tests of motor activity and also can measure aspects of emotional reactivity or habituation on the basis of if, where, and how the animal moves in the arena over time.

The database includes 42 studies that measure motor function and coordination in mammals other than humans (see Figure 21) through assays of behaviors such as locomotor activity [e.g., (Wahlang et al., 2016; Steinberg et al., 2007; Sugawara et al., 2006; Roegge et al., 2004; Nishida et al., 1997; Goldey et al., 1995; Overmann et al., 1987; Bowman and Heironimus, 1981; Bowman et al., 1981; Bowman et al., 1978)], open field [e.g., (Sumathi et al., 2016; Elnar et al., 2012; Curran et al., 2011a; Sugawara et al., 2008; Meerts et al., 2004b; Branchi et al., 2002; Freeman et al., 2000; Pantaleoni et al., 1988; Storm et al., 1981)], rotarod (Bavithra et al., 2017; Sumathi et al., 2016; Nguon et al., 2005a; Nguon et al., 2005b; Fanini et al., 1990; Rosin and Martin, 1981), walking behaviors (Sugawara et al., 2008; Sugawara et al., 2006), and gait analysis (Bushnell et al., 2002; Bruckner et al., 1973). Like humans, rodents exhibit certain motor reflexes in response to stimuli, and alterations in these reflexes can indicate possible disruption of motor neural pathways. Assays that evaluate motor reflexes include surface righting [e.g., (Wei et al., 2015; Tewari et al., 2009; Sugawara et al., 2008; Nguon et al., 2005a; Bowers et al., 2004; Branchi et al., 2002; Bushnell et al., 2002; Gerstenberger and Tripoli, 2001; Pantaleoni et al., 1988; Overmann et al., 1987)], negative geotaxis (Wei et al., 2015; Elnar et al., 2012; Sugawara et al., 2008; Sugawara et al., 2006; Nguon et al., 2005a; Bowers et al., 2004; Branchi et al., 2002; Gerstenberger and Tripoli, 2001; Pantaleoni et al., 1988; Overmann et al., 1987), cliff avoidance (Wei et al., 2015; Sugawara et al., 2008; Sugawara et al., 2006; Pantaleoni et al., 1988), and grasping reflex (Sugawara et al., 2008; Sugawara et al., 2006; Branchi et al., 2002). Motor and coordination tests can be performed in both juvenile and adult animals and are useful in characterizing both developmental and adult exposures (see Figure 24). Overall, the database of studies evaluating PCB exposure and motor activity and coordination in nonhuman mammalian models is quite robust.

Thirteen human studies evaluated PCB levels in biological media (i.e., serum, plasma, blood, cerebrospinal fluid, tissue) during adulthood and endpoints associated with brain aging disorders (see Figure 23). Among these 13 studies, 6 were case-control, 4 were cross-sectional, and 3 were prospective cohort studies. Eight of these studies assessed PCB exposure and Parkinson's disease with varying disease assessment methodology (Raffetti et al., 2020; Hatcher-Martin et al., 2012; Weisskopf et al., 2012; Seegal, 2011; Petersen et al., 2008; Koldkjær et al., 2003; Corrigan et al., 2000; Corrigan et al., 1998). Seven studies assessed PCB exposures and dementia (e.g., Alzheimer's Disease) (Raffetti et al., 2020; Medehouenou et al., 2019; Medehouenou et al., 2014; Hatcher-Martin et al., 2012) or amyotrophic lateral sclerosis (ALS) (Goutman et al., 2019; Vinceti et al., 2017; Su et al., 2016). Overall, the relative paucity of human studies examining PCB exposures and brain aging

disorders, heterogeneity of endpoints assessed, including methodology for endpoint evaluation, and a small number of cases in several studies, indicate the database is unlikely sufficient for hazard identification. No studies meeting PECO in nonhuman mammalian models of brain aging disorders were identified.

Twelve studies evaluated auditory function and PCB exposures in humans (see Figure 21). Half of these were either cross-sectional (Trnovec et al., 2010; Trnovec et al., 2008) or prospective (Koštiaková et al., 2016; Palkovičová Murínová et al., 2016; Sisto et al., 2015; Jusko et al., 2014) performed in (sometimes overlapping) groups of children in eastern Slovakia. These studies used otoacoustic emission testing along with other indicators of auditory function including pure tone audiometry. The remaining references report on prospective studies in birth cohorts from the Netherlands (Vreugdenhil et al., 2004b), the Faroe Islands (Grandjean et al., 2001) and the United States (two related studies performed in the same cohort (Lu et al., 2017; Longnecker et al., 2004)). One study was performed in children from the Yu-Cheng population (Li et al., 2015), and only one study was conducted among adults, in the cross-sectional NHANES survey (Min et al., 2014). Endpoints evaluated in these studies included hearing thresholds and impairment evaluated using audiometry and otoacoustic emissions.

Auditory function was assessed in 15 studies in rats (see Figure 21). Many studies measured auditory thresholds using methods such as reflex modification audiometry, distortion product otoacoustic emissions, and auditory evoked brainstem responses [e.g., (Powers et al., 2009; Powers et al., 2006; Meerts et al., 2004b; Lasky et al., 2002; Herr et al., 2001; Crofton et al., 2000a; Crofton et al., 2000b; Goldey and Crofton, 1998; Herr et al., 1996; Goldey et al., 1995)]. Three studies evaluated the acoustic startle response (ASR), which can provide a relatively crude measure of hearing sensitivity (Nguon et al., 2005a; Bushnell et al., 2002; Overmann et al., 1987); however, an altered ASR might also reflect changes in motor function or emotional state. All 15 studies evaluated developmental PCB exposure via the dam (see Figure 24), including 1 study with a cross-fostering design (Crofton et al., 2000b), which enables evaluation of gestational, lactational, and perinatal exposures independently. Although relatively few studies examined auditory function in PCB-exposed mammals, the existing studies were well conducted, and most used specific and quantitative endpoint evaluation methods. These studies can be used to supplement the human studies of auditory function, especially when evaluating potential effects of developmental PCB exposures.

Changes in brain structure and neurotransmitter levels are thought to contribute to deficits in behavior, including deficits in the behavioral domains discussed above. Fourteen human studies and nine studies in rats or mice evaluated PCB exposure and neurophysiology (e.g., sensory and motor conduction, nerve conduction velocity, event-related potentials) or neuroimaging (see Figure 21, Figure 8). Sixty-nine studies assessed PCB exposures and brain structure at varying levels of biological organization in rats, mice, nonhuman primates, and other nonhuman mammalian species, and 21 studies measured neurotransmitter levels in the brains of PCB-exposed

rats, mice, nonhuman primates, and mink (see Figure 21, Figure 8). These endpoint categories contain more studies evaluating PCB exposures in adult mammals compared with the behavioral domain endpoints (4 human studies of neurophysiology/neuroimaging [see Figure 23], 1 study of neurophysiology in nonhuman mammals [Figure 24], 36 studies of brain structure in nonhuman mammals [see Figure 24], and 14 studies of neurotransmitter levels in nonhuman mammals [see Figure 24]). Eleven studies of neurophysiology or neuroimaging were conducted in human children or adolescents (see Figure 23), and studies evaluating developmental exposure via the dam also comprise a large proportion of the nonhuman mammalian studies in this category (8 studies of neurophysiology, 35 studies of brain structure, and 5 studies of neurotransmitter levels), although a subset of studies assessed brain morphology and neurotransmitter levels following direct juvenile exposure (see Figure 24). Overall, the database contains many studies characterizing PCB exposure and neurophysiology, neuropathology, and neurotransmitters and can be considered robust for hazard identification. However, many endpoints in these categories are more mechanistic and might be most useful for informing subsequent analyses of possible mechanisms/modes of action. Variation in the specific neurotransmitters and histopathological or neurophysiological endpoints evaluated is also considerable; therefore, the comparison of results between studies might be limited. Further, as neuropathology and neurotransmitters are not usually evaluated in humans, and the extent of species differences is not yet fully understood, these data might have unclear human relevance. Another limitation is that not all studies that characterized neurophysiology, brain structure/histology, or neurotransmitter levels also conducted behavioral assays. Therefore, the behavioral correlate(s) of observed molecular changes might yet be unknown.

In summary, the human and nonhuman mammalian databases provide sufficient information to evaluate the potential for PCB-associated nervous system effects in several behavioral domains. Specifically, numerous studies were identified that use well-accepted and validated measures of cognitive function, attention, impulse control, externalizing and internalizing behaviors, motor function, and executive function across the lifespan. In addition, the existing database is likely sufficient to make a determination regarding potential effects of developmental PCB exposures on social cognition and social behavior and auditory function. However, the combined human and nonhuman mammalian databases are likely insufficient to draw conclusions regarding potential PCB-mediated effects on other nervous system endpoint categories.

### 3.3.12. Ocular

Ocular endpoints encompass those that are measured on or in the eye and tissues surrounding the eye. The mammalian eye consists of many parts, including the iris, cornea, pupil, and sclera. Behind the iris and pupil is a lens that focuses light on the back of the eye where it is sensed by the retina. Special cells within the retina transmit electrical signals via the optic nerve to the brain for vision. Periocular tissues include the orbit (the space surrounding the eye), conjunctiva (the mucous membrane covering the inner surface of the eyelids and part of the sclera), tear ducts, and oil glands in the eyelid (i.e., Meibomian glands), which help maintain eye moisture.

Like chloracne, some ocular endpoints, such as Meibomian gland enlargement, ocular discharge, and periorbital edema, are markers of exposure to dioxin-like chemicals (ATSDR, 2000). Other endpoints evaluated with PCB exposure include ocular irritation, abnormal pigmentation of ocular tissues, and conjunctivitis; increased rates of infectious forms of conjunctivitis are considered an indication of increased susceptibility to infection (see Section 3.3.8). Nonhuman mammalian studies also evaluated periocular tissue histopathology. Although periocular endpoints could be perceived as less severe than those evaluated in the eye itself, effects on periocular tissues such as the Meibomian glands can range from minor discomfort to visual impairment (Chhadva et al., 2017).

In the database of studies of PCB exposures, 18 studies in humans and 27 in other mammals evaluated ocular endpoints (see Figure 4). Of the 18 human studies, most are reports following occupational exposures, Yu-Cheng and Yusho poisoning, or other accidental exposures (see Figure 5). These studies generally evaluated endpoints with higher exposures than would occur in the general population. Many of the ocular endpoints were symptoms reported or clinical observations and were not necessarily the focus of the publications. Other human studies included one conducted in an Inuit population (Dewailly et al., 2000) and one cross-sectional study of people living near waste sites (Stehr-Green et al., 1986). Exposures in these studies also could have been higher than those in the general population, and the latter study only evaluated self-reported, physician-diagnosed eye problems without further description.

In the database of studies of PCB exposures, the most commonly studied endpoints were periorbital edema, ocular discharge, Meibomian gland enlargement, ocular irritation, conjunctivitis, and abnormal pigmentation (see Figure 25). In humans, these endpoints were most often evaluated in the Yusho or Yu-Cheng cohorts or in populations with occupational exposures (see Figure 5); these populations could have additional exposures to chemicals other than PCBs that might affect ocular endpoints.

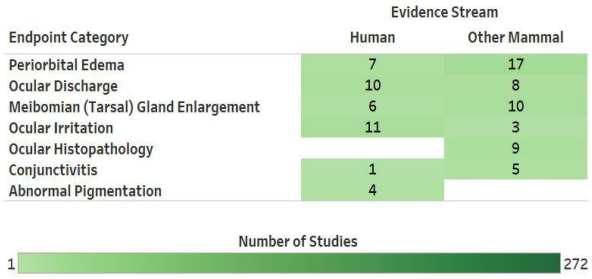


**Figure 25. Overview of Human and Other Mammalian Ocular Studies**

Summary of the database of studies evaluating exposures to PCB mixtures and ocular endpoints organized by endpoint category. Lists of studies included in each count can be accessed via the online interactive version of this figure (https://hawc.epa.gov/summary/visual/assessment/100500282/OverviewAllStudies/). Shading intensity corresponds with the number of studies in each category, from 1 to 272, which is the maximum number of nonhuman mammalian studies in any health endpoint category. The intent is to highlight not only differences in the distribution of studies across ocular endpoint categories but also to emphasize the number of ocular studies relative to the number of studies for other organs/systems.

Most studies available for ocular endpoints were conducted in populations with high PCB exposures (see Figure 5). One was a prospective birth cohort study in Inuit infants exposed via breast milk compared with bottle-fed infants (Dewailly et al., 2000). The focus of this study was susceptibility to infections and immune status in Inuit infants, but nurses screened the children at 3, 7, and 12 months of age for Meibomian gland enlargement and eyelid edema, and the study provided relative risk estimates for conjunctivitis; however, results were based on comparing bottle-fed and breast-fed infants rather than more specific measures of PCB exposure.

Most of the 27 nonhuman mammalian studies (see Figure 4) were conducted in primates, followed by rats, and mice (see Figure 8); 1 study used more than one species (Thomas and Hinsdill, 1978). Of the species evaluated, nonhuman primates are most similar to humans. All studies evaluated ocular endpoints following oral PCB administration (see Figure 9). One study also exposed the animals via inhalation (Casey et al., 1999). Nine nonhuman mammalian studies evaluated ocular histopathology (see Figure 25).

Overall, the human database is limited to endpoints measured following high PCB exposures, including accidental and occupational exposures, and these studies generally provide qualitative information on ocular symptoms. Although most of the human studies evaluated endpoints at high PCB exposure levels in situations for which other exposures were possible, taken together with available data from nonhuman mammalian studies, the database is likely to provide enough information to draw conclusions about the potential for PCB exposure to affect periocular tissues, especially at higher exposure levels.

### 3.3.13. Reproductive

Reproductive endpoints include all those related to the ability to produce a healthy pregnancy, sustain that pregnancy, and produce healthy offspring. Successful reproduction involves direct and indirect interplays among the endocrine, reproductive, and other systems, such that disruption of any of these can lead to adverse reproductive outcomes, defined primarily as failure to conceive, delayed time to pregnancy, and inability to carry a pregnancy to term (i.e., preterm delivery) (Luderer et al., 2019). Several recent reviews and commentaries (Arzuaga et al., 2019; Luderer et al., 2019; Bolden et al., 2017; Sifakis et al., 2017) have proposed approaches to group reproductive endpoints on the basis of either key mechanistic characteristics or functional outcomes; these approaches have both similarities and differences, reflecting the difficulty inherent in grouping such endpoints for both animal and human studies. For this review, female reproductive endpoints are as follows (see Figure 26): sex hormone levels; pubertal development; menstrual cycle characteristics; ovulation; reproductive organ size/weight and histopathology; female anogenital distance; reproductive aging; endometriosis; sexual behavior; female and couple fertility and fecundity (including number of offspring, pregnancy/conception rates, and time to pregnancy [TTP]); gestational length (including preterm birth); pregnancy-related disorders (e.g., preeclampsia, dystocia); and other gynecological disorders (e.g., fibroids and polycystic ovary syndrome [PCOS]). Male reproductive endpoints are as follows: semen and sperm production and

sperm morphology; levels of reproductive hormones; pubertal development; reproductive organ size/weight and histopathology; fertility and fecundity; sexual behavior; male anogenital distance, cryptorchidism, hypospadias, sex ratio of offspring; and erectile dysfunction. Other endpoints related to reproduction, such as endocrine endpoints (see Section 3.3.4) and other developmental endpoints that might occur in the offspring following exposure during pregnancy (including spontaneous abortion and anthropometric measures at birth; see Section 3.3.3), are described elsewhere.

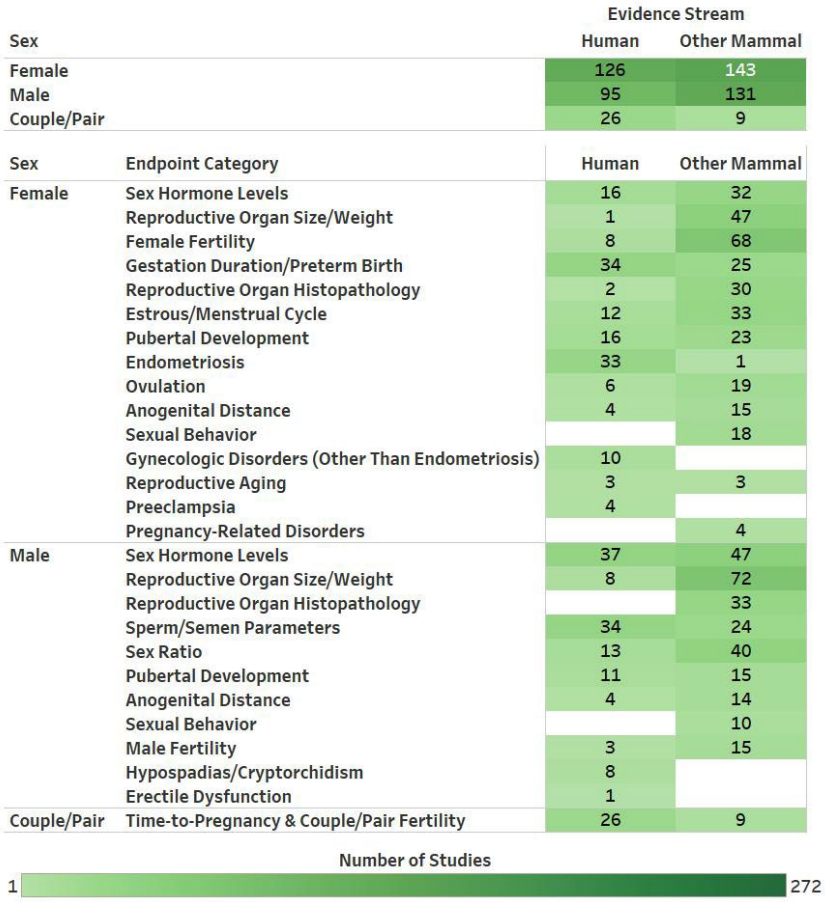


**Figure 26. Overview of Human and Other Mammalian Reproductive Studies**

Summary of the database of studies evaluating exposures to PCB mixtures and reproductive endpoints organized by sex and endpoint category. Lists of studies included in each count can be accessed via the online interactive versions of this figure: (https://hawc.epa.gov/summary/visual/assessment/100500282/OverviewHumanStudies/) for human studies; and (https://hawc.epa.gov/summary/visual/assessment/100500282/OverviewNonhumanMammalStudies/) for studies of nonhuman mammals. The interactive summary of the human database, with the reproductive organ/system filter applied, can be further refined by study design (options: case-control, cohort, cross-sectional, other), population (options: contaminated schools and other buildings, fish/marine mammal (diet), general population, occupational, residents in contaminated area, Yusho/Yu-Cheng), sex (options: couple, female, male), and exposure metric (options: adipose tissue, blood, breast milk, child blood, cord blood, dietary estimates, fish consumption, maternal blood, occupational/JEM, other metric [includes dust and modeled estimates], other tissue). The interactive summary of the nonhuman mammalian database, with the reproductive organ/system filter applied, can be further refined by exposure duration/life stage (options: acute [single dose], chronic, developmental, short-term, subchronic), species (options: cow, ferret, gerbil, guinea pig, mink, mouse, nonhuman primate, rabbit, rat, swine, vole), sex (options: female, male, pair), and exposure route (options: dermal, inhalation, injection, oral). Shading intensity corresponds with the number of studies in each category, from 1 to 272, which is the maximum number of nonhuman mammalian studies in any health endpoint category. The intent is to highlight not only differences in the distribution of studies across reproductive endpoint categories but also to emphasize the number of reproductive studies relative to the number of studies for other organs/systems.

Female reproductive endpoints are related via alterations in the synthesis, production, secretion, or metabolism of sex-steroid hormones (estradiol [E2], progesterone, and testosterone) and gonadotropins (follicle stimulating hormone [FSH] and luteinizing hormone [LH]). Further, many of the endpoints are dependent on each other. For example, some infertility problems can be attributable to endometriosis, which itself can be attributable to alterations in hormone production or immune suppression (Birnbaum and Cummings, 2002). The data available for evaluating PCB exposures and immune function are described in Section 3.3.8. Importantly, the female reproductive system could be affected by exposures occurring not only across the woman's lifespan, but also by intergenerational exposures. Because a woman's primordial ovarian follicles form during her in utero period, exposures occurring to the mother or even grandmother might be instrumental in the development of the reproductive system, especially for factors related to fertility (Hoyer, 2005). Indeed, a recent review finds that at least in animal models, effects of exposures could last for four generations (Nelson et al., 2020). For this reason, multiple-generation studies (animals) and prospective (birth cohort) studies in humans are useful for evaluating female reproductive endpoints. However, studies that evaluate exposure during discrete windows of development can also be useful for identifying windows of susceptibility. For endpoints potentially affected by exposures in either or both members of a couple (TTP, fecundity, and fertility), the most informative study designs are based on preconceptual ascertainment of exposure and prospective follow-up until pregnancy occurs; an excellent example is the Longitudinal Investigation of Fertility and the Environment (LIFE) study (Bloom et al., 2015). Many male reproductive endpoints can be related via the prevailing hypothesis of the testicular dysgenesis syndrome, which states that early life exposure to endocrine disrupting chemicals can disrupt the normal development of fetal germ cells that eventually form the mature male reproductive organs, including sperm production (Skakkebaek et al., 2001). However, male reproductive endpoints can also be sensitive to chemical exposures throughout the lifespan. Regardless of when exposure occurred, endpoints such as production of androgens (such as testosterone), FSH, and LH are clearly related to sperm parameters. Adequate and high-quality sperm are also related to the more "functional" endpoints of fertility/fecundity. Although fertility and fecundity are characteristics of the couple, adequate reproductive function in both partners is necessary (although not sufficient) to produce pregnancy.

With respect to identifying hazard from PCB exposure, the most informative female reproductive endpoints in epidemiological studies are those that are clearly measurable, including age at menarche, menopause, presence of endometriosis, and hormone levels. Important potential confounders for these endpoints include age, body composition, and cooccurring pollutants, especially given the ubiquity of coexposure to other potential endocrine disrupting compounds that could affect female reproductive endpoints (Gore et al., 2015). The most informative male reproductive endpoints observed in humans are also those that are readily measurable for population studies: semen parameters and hormone levels. These endpoints have been routinely measured in epidemiological studies and in clinical settings where infertility evaluations are

performed (Dadhich et al., 2015). Sperm parameters are also among the endpoints considered most sensitive to insult in animal studies, along with histopathology and reproductive organ weights (Mangelsdorf et al., 2003). Other male reproductive endpoints might be less specific and more difficult to evaluate with respect to PCB exposure; for example, erectile dysfunction shares many risk factors with cardiovascular disease (Viigimaa et al., 2020) such as hypertension (de Oliveira and Nunes, 2021) or diabetes mellitus (Kouidrat et al., 2017). Of the endpoints examined with PCB exposure, the most difficult to interpret for female reproduction are those that also rely on the partner, such as fertility/fecundity—information on the male partner is not always available, and the numerous ways these endpoints are parameterized makes it difficult to harmonize findings across studies (Kahn et al., 2021; Hipwell et al., 2019; Smarr et al., 2017). Animal studies can supplement the human database by including a wider array of measurable reproductive endpoints and can be designed to evaluate female- and male-only exposures and exposure of both members of the mating pair.

Of the studies that evaluated PCB exposure and female reproductive endpoints over the lifespan, 126 were human and 143 were other mammalian studies (see Figure 26). In some cases, multiple publications described different endpoints evaluated in the same study population (e.g., the LIFE study). Most human studies of female reproductive endpoints measured PCBs in blood (including cord blood) (see Figure 26). Less commonly, PCBs were measured in breast milk (Rennert et al., 2012; Brucker-Davis et al., 2010; Cao et al., 2008; Khanjani and Sim, 2007; Gladen et al., 2000), follicular fluid (Al-Hussaini et al., 2018; Bloom et al., 2017; Petro et al., 2012), adipose tissue (Pollack et al., 2021; Ploteau et al., 2017; Ploteau et al., 2016; Martínez-Zamora et al., 2015; Trabert et al., 2015; Buck Louis et al., 2012; Qin et al., 2010; Whitcomb et al., 2005) or placenta (Ploteau et al., 2017; Ploteau et al., 2016; Martínez-Zamora et al., 2015; Trabert et al., 2015; Buck Louis et al., 2012; Qin et al., 2010). Some studies characterized PCB exposure using work history (Taylor et al., 1989; Taylor et al., 1984), residence in PCB-contaminated apartments (Kofoed et al., 2021), or reported fish consumption (Lambertino et al., 2011; Mendola et al., 1997; Mendola et al., 1995). Nonhuman mammalian studies included a wide range of experimental designs and life stages of exposure (see Figure 26), including four studies that investigated transgenerational PCB exposure and female reproductive development and fertility for up to three generations through the maternal lineage (Krishnan et al., 2019; Krishnan et al., 2018; Mennigen et al., 2018; Steinberg et al., 2008).

Age at beginning (menarche) and end (menopause) of menstruation was studied in human populations with PCB exposure (Marks et al., 2021; Attfield et al., 2019; Grindler et al., 2015; Croes et al., 2014; Den Hond et al., 2011; Leijs et al., 2008; Chao et al., 2007; Denham et al., 2005; Blanck et al., 2004; Vasiliu et al., 2004; Cooper et al., 2002; Den Hond et al., 2002; Gerhard et al., 1998). Prospective ascertainment for both endpoints is preferred—for menarche, this could mean querying girls (or their parents) as young as 6 years of age, while for menopause, women might be queried beginning at age 40–45 years. Retrospective ascertainment could lead to measurement

error that could be more pronounced with increasing time elapsed. Four studies evaluating age at menarche were prospective cohort studies (Marks et al., 2021; Attfield et al., 2019; Leijs et al., 2008; Vasiliu et al., 2004), while the remainder evaluated age at menarche retrospectively or cross-sectionally (Croes et al., 2014; Den Hond et al., 2011; Chao et al., 2007; Denham et al., 2005; Den Hond et al., 2002; Gerhard et al., 1998). Among the studies that evaluated age at menopause, one was cross-sectional (Grindler et al., 2015), one was conducted within a case-control study of breast cancer (Cooper et al., 2002), and one was conducted within a prospective cohort of women accidentally exposed to polybrominated biphenyls (Blanck et al., 2004). All studies included a wide age range (women younger than 40 years, up to age 74 or older) and relied on self-report of menstruation occurrence. The mammalian database included three studies in rats that evaluated reproductive aging, measured as the onset of persistent vaginal estrus (a syndrome of premature anovulation) (see Figure 26).

Nine human studies [five cross-sectional (Croes et al., 2014; Den Hond et al., 2011; Wolff et al., 2008; Den Hond et al., 2002; Staessen et al., 2001), four cohort (Windham et al., 2015; Su et al., 2012; Leijs et al., 2008; Gladen et al., 2000)] evaluated PCB exposure and markers of female pubertal onset other than age at menarche, such as age at first breast development, age at first pubic hair development, and Tanner stage of breast and pubic hair development (Marshall and Tanner, 1969), in children aged 6–19 years. Most studies assessed Flemish/Dutch populations (Croes et al., 2014; Den Hond et al., 2011; Leijs et al., 2008; Den Hond et al., 2002; Staessen et al., 2001), which might have been exposed to PCBs primarily via waste incineration (Bremmer et al., 1994). In nonhuman mammalian studies, the onset of female puberty (measured as the age at vaginal opening or first estrous) was evaluated in 22 studies in rats and one study in guinea pigs, including four studies that evaluated transgenerational exposures (Krishnan et al., 2019; Krishnan et al., 2018; Mennigen et al., 2018; Steinberg et al., 2008) (see Figure 26). The timing of puberty in rodent models is closely tied to body weight, with delays in puberty resulting from decreases in body weight, so comparison of body weight in control vs. treatment groups in these studies can help distinguish potential direct effects on puberty from a generalized delay in growth. PCB exposure and body weight in early life have been evaluated frequently in rodent models (see Section 3.3.3).

Thirty-three human studies and one study in rhesus monkeys evaluated endometriosis and PCB exposure (see Figure 26), although some human studies were related analyses conducted in the same study population. Eleven of the studies were cross-sectional, one was a cohort, and the remainder were case-control (see Figure 26). One important consideration for this health endpoint is that the most accurate ascertainment is based on surgical assessment (e.g., laparoscopy). Common clinical classification systems include those developed by the American Fertility Study [as used in, e.g., (Buck Louis et al., 2005)] and the American Society for Reproductive Medicine [as used in e.g., (Buck Louis et al., 2012; Niskar et al., 2009)]. All but two studies (Neblett et al., 2020; Fierens et al., 2003) ascertained endometriosis using surgical assessment. However,

misclassification is still a concern, even with these standardized staging systems (Holt and Weiss, 2000). Few studies evaluated other gynecological disorders; one evaluated self-reported "gynecologic disorders" without further detail (Nakamoto et al., 2013), while six studies evaluated uterine fibroids (Wesselink et al., 2021; Neblett et al., 2020; Trabert et al., 2015; Lambertino et al., 2011; Qin et al., 2010; Gerhard et al., 1999), three studies evaluated polycystic ovary syndrome (Neblett et al., 2020; Yang et al., 2015; Vagi et al., 2014), one evaluated adenomyosis (Heilier et al., 2004), and one evaluated pelvic inflammatory disease (Neblett et al., 2020).

Sixteen human studies and 32 studies in other mammals (see Figure 26) measured sex-steroid or gonadotropin levels in females across the lifespan and PCB exposure. Studies of these hormones are particularly important because all female reproductive endpoints described here are related via the synthesis, production, secretion, or metabolism of sex-steroid hormones. The human database included one case-control study, seven cross-sectional studies, and eight cohort studies (see Figure 26). All used standard laboratory methods for hormone measurement. Eight studies evaluated hormones in nonpregnant adult women (Lambertino et al., 2021; Pan et al., 2019; Gallo et al., 2018; Guo et al., 2018; Persky et al., 2011; Windham et al., 2005; Gerhard et al., 1999; Gerhard et al., 1998), with specific information about the timing of collection and menstrual cycle status for premenopausal women, which is crucial to the interpretation of the results. Although some variation occurred in the suite of female reproductive hormones evaluated in these adult populations, most included FSH, LH, and E2 [e.g., (Pan et al., 2019; Gallo et al., 2018; Guo et al., 2018; Miyashita et al., 2018; Kristensen et al., 2016)]. Two studies evaluated reproductive hormones in cord blood at delivery (Warembourg et al., 2015; Takser et al., 2006), while two others evaluated hormones in children 6–9 years of age (Rennert et al., 2012; Su et al., 2012). The measurement of the specific hormones in these younger female populations was less consistent, but both Rennert et al. (2012) and Su et al. (2012) included assessments of E2, testosterone, and others. The mammalian toxicological database consisted of 32 studies in monkeys, rats, mice, mink, rabbits, and guinea pigs (see Figure 26). More than half these animal studies evaluated F1 females that had been exposed during development, including four studies evaluating transgenerational exposures (Krishnan et al., 2019; Krishnan et al., 2018; Mennigen et al., 2018; Steinberg et al., 2008). The hormone measurements varied across nonhuman mammalian studies, including plasma or serum levels of E2, progesterone, testosterone, dehydroepiandrosterone (a precursor to other sex-steroid hormones), FSH, and LH, as well as urinary measurements of estrogen and androgen metabolites. Female anogenital distance, a measure hypothesized to reflect androgenic activity in utero, was investigated in 4 human studies and 15 studies in other mammals (see Figure 26). The human health implications of changes in anogenital distance remain unclear, although some evidence indicates a longer anogenital distance in women might be associated with presence of polycystic ovary syndrome (Sánchez-Ferrer et al., 2017).

Twelve human studies evaluated menstrual cycle irregularities, and six evaluated ovulation (see Figure 26). Nonhuman mammalian toxicology studies evaluated irregularities in the menstrual

cycle (rhesus or cynomolgus monkeys) or estrous cycle (rats, mice, guinea pigs, or cows) or ovulation (rhesus monkeys, rats, mice, rabbits, or mink) (see Figure 26). Some studies also measured sex-steroid hormones or gonadotropins as discussed above, which are integral to the maintenance of the menstrual/estrous cycle and ovulation and are therefore useful for interpreting these endpoints [e.g., (Kristensen et al., 2016; Dickerson et al., 2011; Windham et al., 2005; Meerts et al., 2004a; Gerhard et al., 1999; Bäcklin et al., 1997; Arnold et al., 1993; Truelove et al., 1990; Allen et al., 1980; Jonsson et al., 1975)]. More than half the human studies of menstrual cycle irregularities were cross-sectional (see Figure 26). All but one (Buck Louis et al., 2011a) of the human studies evaluating menstrual cycle length ascertained endpoint information via self-report; this raises the concern for measurement error (Jukic et al., 2007; Small et al., 2007) although such error likely would not differ by exposure status. About half the nonhuman mammalian studies evaluated estrous cyclicity in female rats that had been exposed during development (see Figure 26), including 2 transgenerational studies (Mennigen et al., 2018; Steinberg et al., 2008). Ovulation as measured in nonhuman mammalian studies (e.g., ovulation rates or number of corpora lutea) included evaluations with both adult and developmental exposures.

Numerous human studies evaluated fertility of the woman or the couple (see Figure 26), including studies evaluating time to pregnancy [e.g., (Hwang et al., 2019; Buck Louis et al., 2013; Chevrier et al., 2013; Yang et al., 2008; Axmon et al., 2006; Cole et al., 2006; Toft et al., 2005; Axmon et al., 2004; McGuinness et al., 2001; Buck et al., 2000)] or other measures of couple fertility, such as fertilization rate among couples undergoing IVF [e.g., (Younglai et al., 2002)] or pregnancy rate among couples planning conception [e.g., (Hwang et al., 2019)]. However, as noted above, these studies are difficult to interpret due to the difficulties in disentangling potential effects attributable to exposure status for each partner; a notable exception is the LIFE study in which exposure information was ascertained for each partner (Buck Louis et al., 2011b). The mammalian toxicology literature might help fill this gap, as 68 studies evaluated maternal-only exposure and pregnancy or conception rate (measured as the ability to become pregnant, implantation rates, litter size, or litter number) (see Figure 26), including three transgenerational studies (Krishnan et al., 2018; Mennigen et al., 2018; Steinberg et al., 2008). Female fertility was evaluated in a wide range of species (rhesus monkeys, rats, mice, mink, rabbits, gerbils, ferrets, cows, or swine) (see Figure 26) and was the most commonly measured female reproductive endpoint in the mammalian toxicology literature. Additionally, nine studies evaluated the fertility of mating pairs in rats or mice (see Figure 26).

Thirty-four human studies and 25 studies in other mammals (rhesus monkeys, rats, mice, mink, guinea pigs, ferrets, or cows) evaluated gestational length, including studies of preterm birth (see Figure 26). Most human studies were cohort studies from various countries. Two studies evaluated Yusho or Yu-Cheng patients. Eleven studies evaluated preterm birth as a dichotomous endpoint (Kofoed et al., 2021; Neblett et al., 2020; Bell et al., 2019; Wu et al., 2011; Wojtyniak et al., 2010; Tsukimori et al., 2008; Khanjani and Sim, 2007; Longnecker et al., 2005; Ribas-Fitó et al.,

2002; Berkowitz et al., 1996; Wassermann et al., 1982), which has clear clinical relevance. However, recent research indicates that there might be no threshold for the effect of gestational age on adverse outcomes later in life (Clark et al., 2009; Zhang and Kramer, 2009), which suggests evaluation of gestational length as a continuous endpoint might provide a more sensitive approach to understand potential effects of chemical exposures. Exposure measures used in studies of gestational length and preterm birth spanned a variety of time points; most assessed exposure during pregnancy, while some evaluated exposure within hours or days of delivery (including measures in cord blood, placenta, or dried blood spots) (Bell et al., 2019; Tang et al., 2018; Wu et al., 2011; Brucker-Davis et al., 2010; Wang et al., 2005; Lucas et al., 2004; Ribas-Fitó et al., 2002; Fein et al., 1984) or during early infancy (including measures in breast milk) (Brucker-Davis et al., 2010; Khanjani and Sim, 2007). One study evaluated exposure on the basis of "current" blood measures; time since pregnancy was not reported (Neblett et al., 2020). For these endpoints, the most relevant time window for exposure is during pregnancy.

Pregnancy-related disorders were also reported in a few human and other mammalian studies. In humans, there were four studies of preeclampsia (see Figure 26). One nonhuman mammalian study reported the incidence of dystocia (i.e., difficult or obstructed labor) (Curran et al., 2011b), and three studies reported vaginal bleeding during pregnancy (Lundkvist and Kindahl, 1989; Lundkvist et al., 1987; Brezner et al., 1984). Although these are severe conditions important for public health, the likelihood these databases would support a strong hazard identification conclusion is low.

Two epidemiological studies evaluated PCB exposure and mammographic breast density (Lee et al., 2020; Rusiecki et al., 2020); evaluations of mammary gland differentiation and cell proliferation were also conducted in one rodent study (Brown and Lamartiniere, 1995). Sexual behavior and histopathological evaluations of the uterus, ovaries, and vagina were evaluated only in nonhuman mammalian studies with no human equivalent (see Figure 26). Female sexual behavior was assessed in 18 studies in rats, gerbils, or mink. About half these studies reported only simple measurements of mating incidence or frequency, but four studies in rats assessed specific behavioral indicators of sexual receptivity such as lordosis or latency measurements (Colciago et al., 2009; Steinberg et al., 2007; Chung et al., 2001; Chung and Clemens, 1999), and five studies in rats evaluated sociosexual behavior (i.e., allowing females to choose among stimulus animals with different sex or hormonal status) (Hernandez Scudder et al., 2021; Hernandez Scudder et al., 2020; Topper et al., 2019; Krishnan et al., 2018; Reilly et al., 2018). Changes in sexual behavior are often indicative of hormonal dysregulation but might also be relevant to the evaluation of nervous system function (see Section 3.3.11). Only one epidemiological study evaluated reproductive organ size (uterine length) (Su et al., 2012). By contrast, reproductive organ (e.g., ovary or uterus) weights were widely reported among nonhuman mammalian studies, with fewer studies reporting histopathology of these organs (see Figure 26). Organ weights are considered less informative endpoints due to their nonspecific nature, whereas histopathology can be a relatively sensitive

measurement. Maternal body weight changes, which were measured in many studies that evaluated female fertility [e.g., (Yang et al., 2009; Kostyniak et al., 2005; Kaya et al., 2002; Brunström et al., 2001; Arnold et al., 2000; Hany et al., 1999; Lilienthal et al., 1990; Welsch, 1985; Talcott and Koller, 1983; Thomas and Hinsdill, 1980)], can indicate both maternal toxicity and fetal toxicity, so adjusting for gravid uterine weight can be used to help distinguish potential maternal and intrauterine effects (U.S. EPA, 1991). None of the available studies adjusted for gravid uterine weight; therefore, the maternal body-weight measurements have limited utility for female reproductive hazard identification but could be useful as an indicator of potential overt toxicity when interpreting other endpoints in a study.

Overall, the database of human and nonhuman mammalian studies is likely sufficient to support hazard identification for PCB exposure and female reproductive endpoints. In humans, the endpoints of endometriosis and gestational length have been the most studied. Female fertility was by far the most studied endpoint in the mammalian toxicology literature, but a relatively large number of studies also evaluated other endpoints that can provide further support for assessments of potential human health hazard.

Ninety-five human and 131 other mammalian studies (see Figure 26) evaluated PCB exposure and male reproductive endpoints over the lifespan. In some cases, multiple publications described different endpoints evaluated in the same human study population [e.g., a cohort of Swedish fishermen, e.g., (Rignell-Hydbom et al., 2005b; Rignell-Hydbom et al., 2005a; Rignell-Hydbom et al., 2004)] or subsequent follow-up information from a prospective cohort [e.g., the Russian Children's Study, e.g., (Mínguez-Alarcón et al., 2017; Burns et al., 2016)]. Most human studies of male reproductive endpoints used biomarkers to characterize PCB exposure, with varying numbers of PCB congeners measured in blood (see Figure 26). Less commonly, PCBs were measured in breast milk (Desalegn et al., 2021; Krysiak-Baltyn et al., 2012; Rennert et al., 2012; Brucker-Davis et al., 2008; Cao et al., 2008; Khanjani and Sim, 2007; Gladen et al., 2000), adipose tissue (Koskenniemi et al., 2015; Cok et al., 2009; Çok et al., 2008), placenta (Su et al., 2012; Gladen et al., 2000), or seminal fluid (Lin et al., 2021; Magnusdottir et al., 2005; Rozati et al., 2002; Stachel et al., 1989; Bush et al., 1986), or characterized using a JEM (Rocheleau et al., 2011).

Endpoints related to each other through the framework of the testicular dysgenesis syndrome (i.e., cryptorchidism, hypospadias, anogenital distance, secondary sex ratio) (Skakkebaek et al., 2001) were evaluated in both humans and other mammals (see Figure 26). In general, the studies of cryptorchidism and hypospadias are few and tend to have a small number of cases, which limits the robustness of the overall findings. Male anogenital distance was investigated in 4 human studies and 14 other mammalian studies (see Figure 26). The human health implications of observed changes in anogenital distance remain unclear, although some evidence indicates shorter anogenital distance in men is associated with reduced semen quality (Mendiola et al., 2011). Altered anogenital distance is also associated with an endocrine disrupting impact of other chemical exposures (Kahn et al., 2020). Secondary sex ratio, which is the ratio of male to female

offspring at birth, is a measure of endocrine regulation and disruption during early stages of development. This endpoint was evaluated in 13 human studies and 40 other mammalian studies (see Figure 26). Because secondary sex ratio is a simple endpoint to assess, fairly large sample sizes are available. However, the impact and meaning of these results should be interpreted within the context of data on other clinically relevant endpoints associated with endocrine disruption and reproductive development.

Eleven human studies focused on timing of male pubertal development (see Figure 26). Of these, six evaluated PCBs with adrenarche and gonadarche only (Burns et al., 2016; Den Hond et al., 2011; Humblet et al., 2011; Korrick et al., 2011; Staessen et al., 2001; Gladen et al., 2000), while five others also included hormone measurements (Croes et al., 2014; Grandjean et al., 2012a; Su et al., 2012; Den Hond et al., 2002; Mol et al., 2002), and one additionally reported semen parameters (Mol et al., 2002). Assessment of testicular function is not part of routine examinations in prepubertal males. One recent paper suggests that assessment of anti-Mullerian hormone (AMH; not measured in these studies), inhibin B (measured in Den Hond et al. (2002), Grandjean et al. (2012a), and Meijer et al. (2012)), and testicular volume (measured in Den Hond et al. (2002), Grandjean et al. (2012a), Korrick et al. (2011), and Meijer et al. (2012)), all relatively noninvasive, could be useful for evaluating puberty disorders and primary testicular damage in prepubertal boys and that early diagnosis might be amenable in preventing infertility in adulthood (Condorelli et al., 2018). The mammalian toxicology database on male pubertal development consists of 15 studies in rats (see Figure 26), 10 of which also evaluated sex hormone levels (Krishnan et al., 2019; Topper et al., 2019; Krishnan et al., 2018; Mennigen et al., 2018; Gillette et al., 2017; Walker et al., 2014; Dickerson et al., 2011; Yang et al., 2009; Lilienthal et al., 2006; Meerts et al., 2004a) and one of which additionally reported on sperm concentration (Yang et al., 2009). Most available studies evaluated development of the male reproductive system after gestational exposures (see Figure 26), and endpoints evaluated included preputial separation and testicular descent.

Among studies that focused on adults (past puberty), many reported semen (volume) and sperm (concentration, motility, and morphology) parameters or serum levels of reproductive hormones (see Figure 26). Some overlap occurred, as eight studies reported both types of endpoints (Petersen et al., 2018; Vitku et al., 2016; Petersen et al., 2015; Vested et al., 2014; Haugen et al., 2011; Rignell-Hydbom et al., 2004; Richthoff et al., 2003; Mol et al., 2002). Although many of these studies were cross-sectional (see Figure 26), a few were prospective in nature; for example, the Russian Children's Study evaluated PCB levels measured in mid-childhood, with reproductive endpoints measured up to 10 years later [e.g., (Mínguez-Alarcón et al., 2017)]. Among the cross-sectional studies, many recruited participants from infertility clinics, which could limit the generalizability of findings [e.g., (Paul et al., 2017; Vitku et al., 2016; Abdelouahab et al., 2011; Hauser et al., 2002)]. However, others were conducted among samples with a range of PCB exposure potential, such as Swedish military conscripts (Richthoff et al., 2003) and populations exposed to PCBs through fish consumption [e.g., (Rignell-Hydbom et al., 2005a; Rignell-Hydbom et

al., 2004; Persky et al., 2001)]. For semen and sperm parameters, it is important to consider factors such as place of collection, number of samples collected, abstinence time before collection, and use of standardized laboratory protocols (Cirillo et al., 2011; Brazil et al., 2004; Cohn et al., 2002). Important confounders for semen and sperm parameters can include age and percent body fat, as these are both related to PCB exposure and infertility. Many of the studies of semen and sperm parameters, including those in well-characterized samples of individuals [e.g., (Toft et al., 2006; Rignell-Hydbom et al., 2004; Hauser et al., 2003)], did include age and BMI (along with other potential confounders) in their analyses and, importantly, requested abstinence of two or more days. Timing is also important for hormone measures. For example, morning collection is recommended to account for diurnal variation in serum testosterone concentrations. Studies generally used accepted laboratory protocols for hormone analysis, and although samples were not always consistently collected during morning hours, consideration of timing was often described [e.g., (Vitku et al., 2016; Petersen et al., 2015; Schell et al., 2014; Haugen et al., 2011)].

The mammalian toxicological database for PCB exposure and reproductive hormones and sperm measures consists of 47 and 24 studies, respectively (see Figure 26). Studies that evaluated reproductive hormone levels used several strains of rats and mice, guinea pigs, swine, and rhesus monkeys. Reproductive hormones measured in these studies included testosterone, progesterone, E2, LH, and FSH. Nonhuman mammals were exposed to PCBs during all stages of development, including gestational, peripubertal, and sexually mature life stages. Studies that measured sperm parameters also used a variety of mammalian models, including rats, mice, and rhesus monkeys, and most exposed peripubertal or sexually mature animals (see Figure 26). Endpoints considered in these studies included sperm count, motility, production, concentration, abnormalities, and in vitro fertilizing ability.

Three human studies evaluated male infertility and PCB exposure (see Figure 26). Although numerous studies of couple fertility and fecundity were identified, relatively few considered paternal PCB exposure along with maternal exposure, including studies conducted among male partners in the New York State Angler Cohort (Buck et al., 2000; Buck et al., 1999) and the LIFE study (Hwang et al., 2019; Zhang et al., 2019; Buck Louis et al., 2013). Only one cross-sectional study evaluated erectile dysfunction (see Figure 26). The mammalian toxicology database on male fertility endpoints consists of 15 studies evaluating implantations, mating and pregnancy index, litter size and number in unexposed females mated to exposed males (see Figure 26). Experimental models used in these studies include rats, mice, mink, and rhesus monkeys.

Measures of reproductive organ size and weight can be used to detect changes in levels or responsiveness to reproductive hormones (Dent et al., 2015; Habert et al., 2014). There were 8 human studies that evaluated reproductive organ size in males, by measuring testicular volume. One of these was conducted in very young children (< 2 years of age) (Meijer et al., 2012), while the remaining studies evaluated testicular volume as a measure of pubertal development (Burns et al., 2016; Grandjean et al., 2012a; Humblet et al., 2011; Korrick et al., 2011; Den Hond et al., 2002; Mol

et al., 2002; Staessen et al., 2001). Seventy-two studies evaluated PCB exposures and reproductive organ weights in a variety of species and strains of mammals, including mice, rats, rabbits, rhesus monkeys, mink, guinea pigs, ferrets, voles, and swine (see Figure 26).

Additional male reproductive endpoints evaluated only in nonhuman mammalian studies with no human equivalent include sexual behaviors and histopathology (see Figure 26). Sexual behaviors such as mating index, frequency of intromissions, and latency in ejaculations were evaluated in 10 studies in rats, mice, or mink. Male reproductive organ histopathology was evaluated in 33 studies that examined testes and accessory reproductive organs (e.g., prostate, seminal vesicle, epididymis) in different species and strains of mammals, including rats, rabbits, mice, guinea pigs, swine, rhesus monkeys, and mink. Studies that evaluated histopathology or organ weights exposed mammals to PCBs during all stages of development, including gestational, peripubertal, and sexually mature life stages.

Overall, the human and nonhuman mammalian databases are likely to provide sufficient information to determine whether a hazard exists for male reproductive development, with the most informative endpoints evaluated in humans being semen and sperm parameters and levels of male reproductive hormones. Relatively few human studies examined paternal PCB exposure in relation to fertility and fecundity, but this potential association was examined in 15 nonhuman mammalian studies (see Figure 26). Reproductive organ weights and hormonal measures were the most studied endpoints in the mammalian toxicology literature, but numerous studies using diverse experimental models and designs evaluated other endpoints that can provide further support for hazard assessment and could address gaps in the human database.

### 3.3.14. Respiratory

The respiratory system includes the upper respiratory tract (nose, nasal cavity, sinuses, larynx, and trachea) and lower respiratory tract (lungs, bronchi and bronchioles, and alveoli). Through gas exchange in the lung, the respiratory system supplies oxygen to the blood, where it is transported to the tissues, and removes carbon dioxide carried in the blood from the tissues. Respiratory health is assessed through measurements of pulmonary structure (e.g., lung weight, histopathology, and chest radiography), pulmonary function (e.g., lung volume and air flow), or respiratory symptoms (e.g., shortness of breath, cough, presence of sputum, and chest tightness). The main measures of pulmonary function are determined by spirometry and include forced vital capacity (FVC), forced expiratory volume in the first second of the forceful exhalation (FEV1), and FEV1/FVC ratio; lung volume, diffusing capacity, and exercise testing are also common measures. Other parameters of pulmonary health include measures of respiratory sounds, sputum analysis, and blood gas tension. Respiratory endpoints related to asthma or infectious respiratory diseases are discussed in Section 3.3.8. Environmental exposures to chemicals can cause impaired lung development and function in children or diminished lung function in adults, and the effects of these exposures might depend on individual response to oxidative stress and inflammation (Cao et al., 2016; Spann et al., 2016). Several factors can influence the potential for respiratory effects of

exposure to chemicals, including sex, age, genetic factors, medical history (e.g., perinatal exposures and outcomes, childhood asthma, and immune system health), active smoking, occupational or ambient air pollution, diet (pro- and antioxidant intake), physical activity, and fitness (Cao et al., 2016).

Among the studies under consideration as relevant for PCB hazard identification, both human and other mammalian studies evaluated respiratory endpoints (see Figure 4). Human studies included inhalation or dermal exposure in occupational settings [e.g., (Kimbrough et al., 2015; Gustavsson and Hogstedt, 1997; Brown et al., 1991; Fitzgerald et al., 1989; Emmett et al., 1988b; Emmett et al., 1988a; Gustavsson et al., 1986; Lawton et al., 1986; Brown and Jones, 1981; Fischbein et al., 1979)] and in proximity to three chemical waste sites (Stehr-Green et al., 1986), oral exposure through ingestion of contaminated rice bran oil (Yusho patients) (Kanagawa et al., 2008; Nakanishi et al., 2005; Tokunaga and Kataoka, 2001; Hirota et al., 1995; Nakanishi et al., 1985; Shigematsu et al., 1978), and general population exposures assessed in early life (Abellan et al., 2019; Leijs et al., 2018; Hansen et al., 2015). Although most nonhuman mammalian studies exposed animals by the oral route, exposure also occurred via injection, inhalation, and dermal contact (see Figure 9). A few human studies assessed pulmonary function, histopathology, chest radiography, respiratory sounds, and sputum analysis (see Figure 27). Related endpoints assessed in nonhuman mammalian studies included pleural effusion, respiratory rate, blood gas tension, pulmonary histopathology, and lung weight.

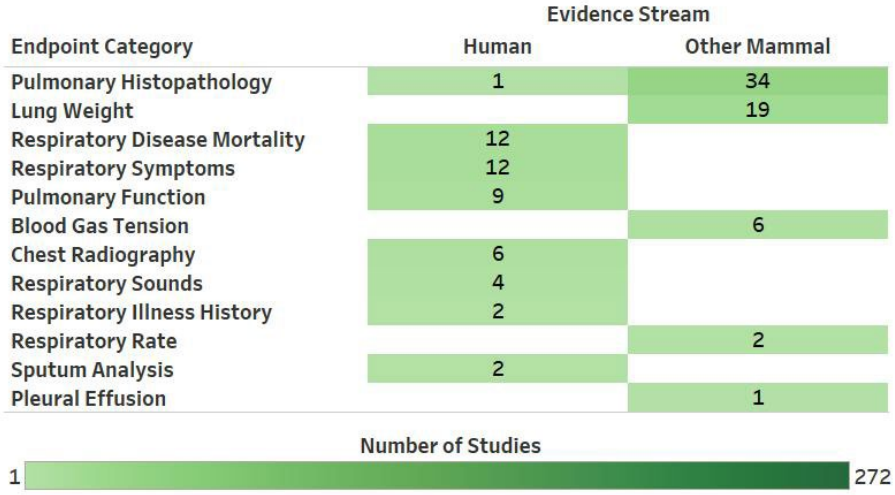


**Figure 27. Overview of Human and Other Mammalian Respiratory Studies**

Summary of the database of studies evaluating exposures to PCB mixtures and respiratory endpoints organized by endpoint category. Lists of studies included in each count can be accessed via the online interactive version of this figure (https://hawc.epa.gov/summary/visual/assessment/100500282/OverviewAllStudies/). Shading intensity corresponds with the number of studies in each category, from 1 to 272, which is the maximum number of nonhuman mammalian studies in any health endpoint category. The intent is to highlight not only differences in the distribution of studies across respiratory endpoint categories but also to emphasize the number of respiratory studies relative to the number of studies for other organs/systems.

Of the human studies in the database, three assessed lung function in the general population (Abellan et al., 2019; Leijs et al., 2018; Hansen et al., 2015). Hansen et al. (2015) examined prenatal exposure to PCBs and allergic sensitization and lung function in 20-year-old offspring in a Danish cohort of pregnant women. Abellan et al. (2019) examined prenatal exposure to PCBs and lung function during childhood, while Leijs et al. (2018) assessed PCB serum levels and lung function in adolescence, controlling for perinatal exposure to PCDD (polychlorinated dibenzodioxins). An additional human study focused on respiratory symptoms in a small sample of participants living in proximity to three chemical waste sites (Stehr-Green et al., 1986). The remaining studies in the database assessed occupational exposure to PCBs or were conducted among the Yusho cohort (see Figure 5). These studies targeted populations exposed to much higher levels of total PCBs than the general population; and, as Nakanishi et al. (2005) noted, PCDFs, not PCBs, have been shown to be "the major causative agents of Yusho" in more recent studies (see Section 3.2.1). Additionally, of the Yusho studies, only one was a longitudinal analysis (Nakanishi et al., 2005), while the others were cross-sectional analyses and thus less informative for PCB hazard identification.

Most of the 49 nonhuman mammalian studies (see Figure 4) were conducted in rodent models such as rats, mice, and guinea pigs (see Figure 8). Seven studies used nonhuman primates as their animal model. Nonhuman primates have the most similar respiratory system structure to humans, which allows for the collection of endpoints such as pulmonary function tests (Miller et al., 2017a) that are unattainable using other mammalian models. Pulmonary histopathological evaluation, which was conducted in 34 nonhuman mammalian studies across a variety of species (see Figure 27, Figure 8), might be useful as a complement to data from human studies. Lung weight, measured in 19 nonhuman mammalian studies, has been shown to be correlated with histopathological changes (Wahlström et al., 2013), which suggests that this marker is a useful indicator for potential lung injury.

Some human studies only assessed respiratory disease mortality or respiratory symptoms/illness history in the absence of other more specific measures of respiratory function (Fitzgerald et al., 1989; Emmett et al., 1988b; Stehr-Green et al., 1986; Smith et al., 1982; Fischbein et al., 1979). In nonhuman mammalian studies, measurements of blood gas tension and respiratory rate were recorded (see Figure 27). Although these endpoints have been used to help diagnose human patients with acute lung injury or acute respiratory distress syndrome, they are not the most specific measurements of respiratory health. Collectively, these human and other mammalian studies are less informative for PCB hazard identification because they capture a broad range of conditions with potentially unrelated etiologies.

Overall, the human database is mostly limited to populations with high PCB exposure, some with simultaneous exposures to other compounds that could contribute to potential effects. However, the combined human and other mammalian database is likely to provide enough information to draw conclusions about the potential for PCB exposure to cause respiratory effects, especially at relatively high exposure levels.

### 3.3.15. Urinary System

The kidney and lower urinary tract (ureters, bladder, and urethra) make up the mammalian urinary system. The kidney primarily eliminates metabolic waste products but plays other important physiological roles including control of body fluid volume, electrolyte regulation, protein and hormone recycling, and other metabolic processes (Frazier et al., 2012; Tesch, 2010). The lower urinary tract primarily transports (and stores) urine from the kidney for elimination (Frazier et al., 2012).

In the kidney, pathophysiological responses to chemical exposures can range from subclinical elevations in urinary or serum levels of certain biomarkers (e.g., creatinine) to frank disease, including renal failure. Among the 29 human studies of PCB exposure and urinary system endpoints (see Figure 4), four evaluated PCB exposures and frank disease. Two studies evaluated diabetic nephropathy in NHANES participants (Everett and Thompson, 2016, 2014), while the remaining studies evaluated self-reported kidney disease in a Japanese general population sample (Nakamoto et al., 2013) and diabetic end stage renal disease among American Indians (Grice et al., 2017). In this latter study, serum levels of numerous PCB congeners were measured and evaluated using a nested case-control design. The prospective nature (PCBs collected at baseline, diabetes status followed over 10 years) and large number of PCBs evaluated lend additional confidence that this study can provide useful information about the potential for PCB exposure to affect kidney function.

Although the number of human studies of the most severe endpoints is small, the results can be evaluated in parallel with the results of studies in nonhuman mammals exposed to PCB mixtures. In animals, kidney damage can be evaluated directly using histological methods, and kidney histopathology is one of the most commonly evaluated urinary system endpoints in the PCB database. However, investigations of diabetic nephropathy are unique to the epidemiological database. Although diabetic animals can develop kidney disease that resembles human diabetic nephropathy, currently available animal models cannot fully recapitulate diabetic renal changes between humans and animals (Azushima et al., 2018; Velasquez et al., 1990), making this a potentially promising yet challenging area of study.

Although nephropathy and kidney disease can be considered more severe manifestations of kidney pathology, most of the human studies identified did not evaluate frank disease, but instead measured biomarkers of urinary system function (see Figure 28). The most common biomarker endpoints included serum levels of uric acid, urinary or serum creatinine, blood urea nitrogen (BUN), and urinary albumin. All are used in clinical practice but might also be useful to detect sub- or preclinical changes in kidney function in epidemiological studies (Gounden et al., 2021; Hernandez Scudder et al., 2021; Lopez-Giacoman and Madero, 2015). For example, increased albumin levels are considered a sensitive marker of chronic kidney disease, although not specific to a single cause. Increased BUN is likewise a general marker of decreased kidney function, but can vary with diet, medication (steroid) use, and other factors. Creatinine is thought to be a more

accurate proxy for glomerular filtration rate (GFR; considered a "gold standard" measure of kidney function) than BUN, although it can vary widely within an individual depending on factors such as diet and changes in muscle mass. Because of the potential lack of sensitivity and specificity of individual biomarkers of renal function, studies evaluating multiple biomarkers (or ratios) [e.g., (Serdar et al., 2014; Yoshimura et al., 2005; Emmett et al., 1988a; Lawton et al., 1985; Baker et al., 1980; Fischbein et al., 1979)], might provide greater evidence for meaningful health outcomes compared with studies only evaluating a single biomarker in isolation. A general consideration for studies using biomarkers of urinary system function is that serum levels of PCBs could theoretically be elevated due to reduced GFR that developed due to an unrelated cause. Prospective studies that evaluate PCB exposure prior to development of any decrements of urinary system function are the best way to address this concern, but most studies identified were cross-sectional in design (see Figure 6). Biomarkers of renal function, including urinary or serum creatinine and BUN, also were examined in 28 nonhuman mammalian studies, which can provide additional information useful for evaluating potential causal relationships between exposure and effect (see Figure 28).

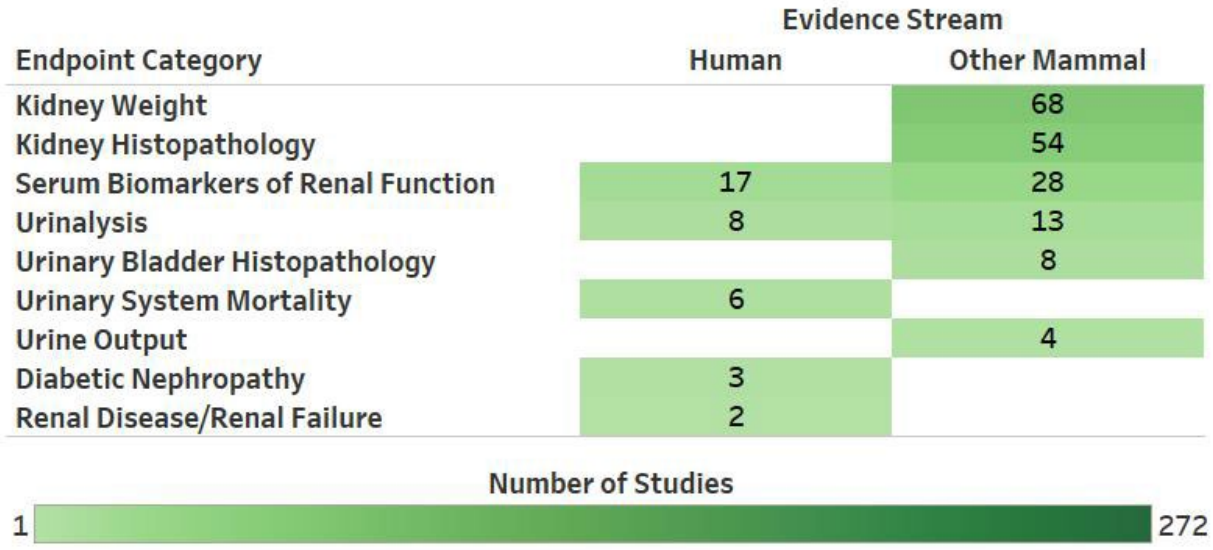


**Figure 28. Overview of Human and Other Mammalian Urinary System Studies**

Summary of the database of studies evaluating exposures to PCB mixtures and urinary system endpoints organized by endpoint category. Lists of studies included in each count can be accessed via the online interactive version of this figure (https://hawc.epa.gov/summary/visual/assessment/100500282/OverviewAllStudies/). Shading intensity corresponds with the number of studies in each category, from 1 to 272, which is the maximum number of nonhuman mammalian studies in any health endpoint category. The intent is to highlight not only differences in the distribution of studies across urinary system endpoint categories but also to emphasize the number of urinary system studies relative to the number of studies for other organs/systems.

Six human studies evaluated urinary system-related mortality (see Figure 28); all were conducted among exposed workers and relied mainly on duration of employment as a proxy for magnitude of PCB exposure. The study populations for these six analyses were sometimes

overlapping but covered different periods. Causes of death evaluated included general death due to disorders of the genitourinary system and more specific causes such as nephritis and renal sclerosis.

In addition to the endpoints described above, studies of nonhuman mammals exposed to PCB mixtures also evaluated kidney weight and urine composition and output (see Figure 28). According to Craig et al. (2015), absolute kidney weight and renal histopathology are correlated, making kidney weight a suitable marker to detect potential renal impacts from chemical exposure. Measurements of urinary components relevant for assessing urinary system hazard included urinary proteins, electrolytes, pH, blood, ketones, urea, and other excretory products (e.g., sediment, casts). Urine output was infrequently studied following PCB exposure, limiting the potential utility of these results for PCB hazard identification.

The bulk of available studies in the database evaluated PCB exposures and kidney structure and function, but the urinary system also includes the urinary bladder. The lower urinary system (ureter, bladder, urethra) is composed of similar tissue types (urothelium, connective tissue, and muscle), which can be a primary target of xenobiotics but can also be altered by the production of urinary solids (Frazier et al., 2012). Urinary bladder histopathology has been evaluated in eight nonhuman mammalian studies (see Figure 28); five of these evaluated kidney and urinary bladder histopathology together (Arnold et al., 1997; Schaeffer et al., 1984; Chu et al., 1980; Iatropoulos et al., 1978; Koller and Zinkl, 1973), which allows for a limited assessment of potential linkages among health endpoints observed across the full urinary system.

Multiple human and nonhuman mammalian studies evaluated urinary system endpoints. Clinical evaluations of serum and urinary biomarkers of renal function are available from both types of studies, providing a foundation for evaluating potential hazard for these endpoints. Other important endpoints, like nephropathy and kidney disease/failure, were infrequently studied in human populations. However, nonhuman mammalian studies offer supporting hazard information, including evaluations of kidney weight and histopathology. In contrast, no human studies and very few nonhuman mammalian studies evaluated endpoints related to the urinary bladder, which represents an area of uncertainty that would benefit from further research.

# 4. CONCLUSIONS

In this review, over 1,500 studies of humans and other mammals exposed to PCB mixtures were mapped to 15 organs/systems. We identified 637 mammalian toxicological studies evaluating endpoints in a variety of species exposed for different durations and at different life stages and 953 epidemiological studies conducted using diverse populations and methods. Although human and other mammalian data are abundant for some organs/systems (e.g., hepatobiliary, nervous system, and reproductive), some endpoints of great public interest (e.g., cardiovascular disease, autism) have not been extensively studied in the context of PCB mixture exposure (see Table 3[1]).

Table 3 provides a high-level summary of the endpoints in each organ/system that were evaluated in human studies, along with preliminary assessments of the informativeness of each database that consider the availability of both human and other mammalian studies. More informative databases are more likely to support conclusive systematic reviews, while less informative databases could be used to identify important topics for future research. Endpoints identified as having low specificity might be most useful when evaluated in combination with other, more informative measures. The anthropocentric focus of Table 3 was chosen for simplicity and because endpoints grounded in strong human and other mammalian data provide the most informative basis for hazard identification. However, endpoints evaluated only in animals can and often do provide sufficient evidence to support the identification of hazards and analysis of dose-response relationships critical for risk assessment (U.S. EPA, 2022). Notably, sparse data exist for inhalation and dermal exposures in both humans and other mammals, representing important areas of uncertainty that would benefit from further research, especially because these are highly relevant human exposure routes.

There are several considerations that are important for interpreting this work. First, it relies on publicly accessible published data. Supplemental search strategies (e.g., searching reference lists of reviews, citation mapping, gray literature searches) were not extensively applied, but technical experts did identify a few additional references for screening (n = 25). Historically, scientific journals have often enforced publication length restrictions, sometimes leading to incomplete reporting of study results. Potential selective reporting, where authors fail to mention they conducted an evaluation or fail to report the results of an evaluation, is a factor to consider at

[1]This table provides an overview of the available data relevant for evaluating select endpoints within each organ/system, with a focus on endpoints evaluated in human studies. Preliminary assessments of the potential informativeness of each database are included, with availability of evidence from nonhuman mammalian studies contributing to those assessments. Endpoints measured only in nonhuman mammalian models are not included in this table to reduce the complexity of the analysis and to focus on the endpoints with the most direct human relevance.

the study evaluation step of a full systematic review. Furthermore, journals have been somewhat reluctant to publish reports with primarily null results (Mlinarić et al., 2017), and some work might not have been published on the basis of decisions made by study sponsors or other factors (Bero et al., 2016). Publication bias exists when the reasons behind a failure to publish are associated with the direction or magnitude of the effects observed (Dwan et al., 2013; Dwan et al., 2008). Our analysis of the PCB database included only published reports and did not address the potential for publication bias. Future systematic reviews stemming from this work could consider using statistical approaches to assess publication bias for studies of health endpoints and exposure to PCB mixtures (Dalton et al., 2016). Another caveat is that this evidence map is based only on full-text screening and preliminary data extraction. Future analyses could include study evaluation and full extraction of the data from subsets of studies relevant for specific research questions. These additional review steps are needed to develop strong conclusions linking PCB exposure with potential health effects. For example, full data extraction would be required to examine the magnitude of exposure in animal studies relative to anticipated human exposures, which is an important consideration for both hazard identification and dose-response assessment. Of note, another challenge in conducting systematic reviews of large complex databases involves the use of multiple systematic review tools, continual duplicate removal, and an ever-increasing literature base as new studies are published each year.

The primary goal of this evidence map was to use systematic review methods to identify, summarize, organize, and disseminate data relevant for characterizing potential human health concerns from exposure to PCB mixtures. As an important part of this effort, we developed interactive figures to help readers explore the available literature, including the ability to create lists of references with customized combinations of study design features based on the specific interests of the individual user. By sharing information from this SEM in this way, we hope to provide a valuable tool that will both support future risk assessment work and highlight areas of uncertainty that can be prioritized in future research to advance our understanding of PCB mixtures and their potential effects on health.

**Table 3. Overview of the databases available for selected endpoint categories by organ/system**

| Organ/system | More informative endpoint categories | Less informative endpoint categories | Notes |
|---|---|---|---|
| Cardiovascular | Blood pressure/Hypertension<br>IHD (including myocardial infarction)<br>Cerebrovascular disease (including stroke) | *More data needed*:<br>Atherosclerosis and other vascular diseases<br>Heart failure<br>Fetal heart rate<br><br>*Low specificity or sensitivity*:<br>Cardiovascular disease (NOS)<br>Subjective complaints | Cholesterol/triglyceride levels were classified as hepatobiliary endpoints (Section 3.3.7) |
| Dermal | Acne/Chloracne<br>Abnormal pigmentation<br>Dermal irritation (including eczema)<br>Hyperkeratosis<br>Nail deformities | More data needed:<br>Periodontal disease (including gingival swelling/recession)<br>Scar formation<br><br>*Low specificity or sensitivity*:<br>"Skin problems" | Most human studies evaluated endpoints at high PCB exposure levels<br><br>Atopic eczema was classified as an immune endpoint (Section 3.3.8); dental abnormalities were classified as musculoskeletal endpoints (Section 3.3.10) |
| Developmental | Weight and size (early life) | *More data needed*:<br>Miscarriage/stillbirth<br>Birth defects<br><br>*Low specificity or sensitivity*:<br>Placental weight/histology | Measures of gestation length, pubertal development, and endpoints associated with testicular dysgenesis syndrome were classified as reproductive endpoints (Section 3.3.10) |
| Endocrine | Thyroid function | *More data needed*:<br>Thyroid disease<br>Adrenal gland function<br>Other endocrine organs and hormones (including parathyroid endpoints) | Sex hormone levels were classified as reproductive endpoints (Section 3.3.13); insulin levels were classified as metabolic endpoints (Section 3.3.9 |

| Organ/system | More informative endpoint categories | Less informative endpoint categories | Notes |
|---|---|---|---|
| Gastrointestinal | (none) | *More data needed*:<br>Gastric ulcer<br>Colorectal polyps<br>Abdominal ultrasonography<br><br>*Low specificity or sensitivity*:<br>Abdominal pain<br>Nausea/vomiting<br>Changes in bowel habits<br>Bloating<br>Indigestion<br>Loss of appetite | Database limited for hazard assessment |
| Hematopoietic | WBC counts<br>Red blood cell counts/Hemoglobin | *More data needed*:<br>Anemia<br>Clotting function<br>Platelet counts<br><br>*Low specificity or sensitivity*:<br>Blood disease mortality | Measures of WBC function were classified as immune endpoints (Section 3.3.8) |
| Hepatobiliary | Liver disease (including cirrhosis and steatosis)<br>Serum biomarkers of liver function<br>Cholesterol/Triglyceride levels<br>Liver enzyme induction | More data needed:<br>Porphyria<br>Gallbladder and biliary endpoints<br><br>*Low specificity or sensitivity*:<br>Hepatomegaly | |
| Immune | Immune suppression (including susceptibility to infection, antigen-specific antibody responses, WBC function, DTH)<br>Atopy (including allergies/asthma) | *More data needed*:<br>Autoimmunity (especially autoimmune disease incidence)<br><br>*Low specificity or sensitivity*:<br>Nonspecific immunoglobulin levels<br>WBC counts<br>Immune organ size/weight | WBC counts were classified primarily as hematopoietic endpoints (Section 3.3.6) |

| Organ/system | More informative endpoint categories | Less informative endpoint categories | Notes |
|---|---|---|---|
| Metabolic | Glucose homeostasis (including IR, IGT/prediabetes, Type 2 diabetes mellitus, gestational diabetes) | *More data needed*:<br>Metabolic rate<br><br>*Low specificity or sensitivity*:<br>Metabolic syndrome<br>Diabetes mellitus (NOS)<br>Overweight/obesity | Cholesterol/triglyceride levels were classified as hepatobiliary endpoints (Section 3.3.7); Type 1 Diabetes was classified as an immune endpoint (Section 3.3.8); diabetic nephropathy was classified as a urinary system endpoint (Section 3.3.15) |
| Musculoskeletal | Bone density/strength<br>Dental abnormalities (including enamel defects and dental caries) | *More data needed*:<br>Arthritis<br><br>*Low specificity or sensitivity*:<br>Musculoskeletal complaints (including muscle/joint pain, muscle weakness) | Most human studies evaluated endpoints at high PCB exposure levels, especially in fish-consuming populations<br><br>Rheumatoid arthritis was also classified as an immune endpoint (Section 3.3.8) |
| Nervous System | Cognitive function<br>Attention, impulse control, externalizing and internalizing behaviors<br>Executive function<br>Motor function/development<br><br>Following developmental exposures:<br>Social cognition and behavior<br>Auditory function | *More data needed*:<br>Brain aging disorders<br>Visual function<br>Olfactory function<br>Neurophysiology/neuroimaging<br>Following exposures during adulthood:<br>Social cognition and behavior<br>Auditory function<br><br>*Low specificity or sensitivity*:<br>Dizziness<br>Headache<br>Fatigue/level of consciousness<br>Neurological condition<br>Neurological disease mortality<br>Peripheral sensation or pain<br>Play behavior<br>Sleep problems | |
| Ocular | Ocular swelling and irritation (including periorbital edema, ocular discharge, Meibomian gland enlargement, conjunctivitis) | | Most human studies evaluated endpoints at high PCB exposure levels<br><br>Infectious forms of conjunctivitis were classified as immune endpoints (Section 3.3.8) |

| Organ/system | More informative endpoint categories | Less informative endpoint categories | Notes |
|---|---|---|---|
| Reproductive | Sex hormone levels<br>Fertility<br>Sperm/semen parameters<br>Gestation length (including preterm birth)<br>Endometriosis<br>Pubertal development<br>Endpoints associated with testicular dysgenesis syndrome (including anogenital distance, hypospadias, cryptorchidism, sex ratio) | *More data needed*:<br>Gynecological disorders other than endometriosis<br>Pregnancy-related disorders (including preeclampsia)<br>Menstrual cycle characteristics<br>Ovulation<br>Reproductive aging<br><br>*Low specificity or sensitivity*:<br>Erectile dysfunction | Measures of birth defects, miscarriage/stillbirth, and placental health were classified as developmental endpoints (Section 3.3.3) |
| Respiratory | Pulmonary health and function (including chest radiography, spirometry, respiratory sounds, sputum analysis) | *Low specificity or sensitivity*:<br>Respiratory disease mortality<br>Respiratory illness history<br>Respiratory symptoms (e.g., shortness of breath, cough/sputum, chest tightness) | Most human studies evaluated endpoints at high PCB exposure levels<br><br>Asthma and infectious respiratory diseases were classified as immune endpoints (Section 3.3.8) |
| Urinary System | Biomarkers of renal function (including markers measured in serum or urine) | *More data needed*:<br>Kidney disease/renal failure (including diabetic nephropathy)<br>Urinary system components other than the kidneys<br><br>*Low specificity or sensitivity*:<br>Urinary system mortality (NOS) | |

DTH = delayed type hypersensitivity; IGT = impaired glucose tolerance; IR = insulin resistance; IHD = ischemic heart disease; NOS = not otherwise specified; PCB = polychlorinated biphenyl; WBC = white blood cell.

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# APPENDIX A. QUALITY ASSURANCE FOR A SYSTEMATIC EVIDENCE MAP FOR POLYCHLORINATED BIPHENYL (PCB) MIXTURES: EVALUATION OF NONCANCER HEALTH ENDPOINTS AND EXPOSURES

This product is prepared under the auspices of the U.S. Environmental Protection Agency (EPA) within the Office of Research and Development (ORD) in the Center for Public Health and Environmental Assessment (CPHEA). EPA has an agency-wide quality assurance (QA) policy that is outlined in the *EPA Quality Manual for Environmental Programs* (see CIO 2105-P-01.1) and follows the specifications outlined in EPA Order CIO 2105.1.

As required by CIO 2105.1, ORD maintains a Quality Management Program, which is documented in an internal Quality Management Plan (QMP). The latest version was developed in 2013 using Guidance for Developing Quality Systems for Environmental Programs (QA/G-1). A National Center for Environmental Assessment (NCEA)/CPHEA-specific QMP was also developed in 2013 as an appendix to the ORD QMP. QA for products developed within CPHEA is managed under the ORD QMP and applicableappendices.

This work was conducted under the U.S. EPA Quality Assurance program to ensure data are of known and acceptable quality to support their intended use. Surveillance of the work by the lead authors and programmatic scientific leads ensured adherence to QA processes and criteria, as well as quick and effective resolution of any problems. The QA manager, lead authors, and programmatic scientific leads have determined under the QA program that this work meets all U.S. EPA quality requirements. This report was written with guidance from the CPHEA Quality Assurance Project Plans (QAPPs; see table below). As part of the QA system, a quality product review is conducted prior to management clearance. A Technical Systems Audit may be performed at the discretion of the QA staff. This project underwent three quality audits in 2020, 2021, and 2022, with no major findings. The report was subject to internal peer review by two CPHEA scientists and an independent external peer review by three scientific experts. The reviews focused on whether all studies were correctly selected, interpreted, and adequately described for the purposes of this report. The reviews also covered quantitative and qualitative aspects of the report and addressed whether uncertainties were adequately characterized.

| Title | Document number | Latest approval date |
|---|---|---|
| Program Quality Assurance Project Plan (PQAPP) for the Integrated Risk Information System (IRIS) Program | L-CPAD-0030729-QP-1-5 | June 2022 |
| Quality Assurance Project Plan (QAPP) General Support of CPHEA Human Health Assessment Activities | L-CPAD-0031961-QP-1-2 | May 2022 |
| Quality Assurance Project Plan (QAPP) Support for the IRIS Toxicological Review of Polychlorinated Biphenyls (PCBs): Effects Other Than Cancer | L-CPAD-0031956-QP-1-2 | July 2021 |

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