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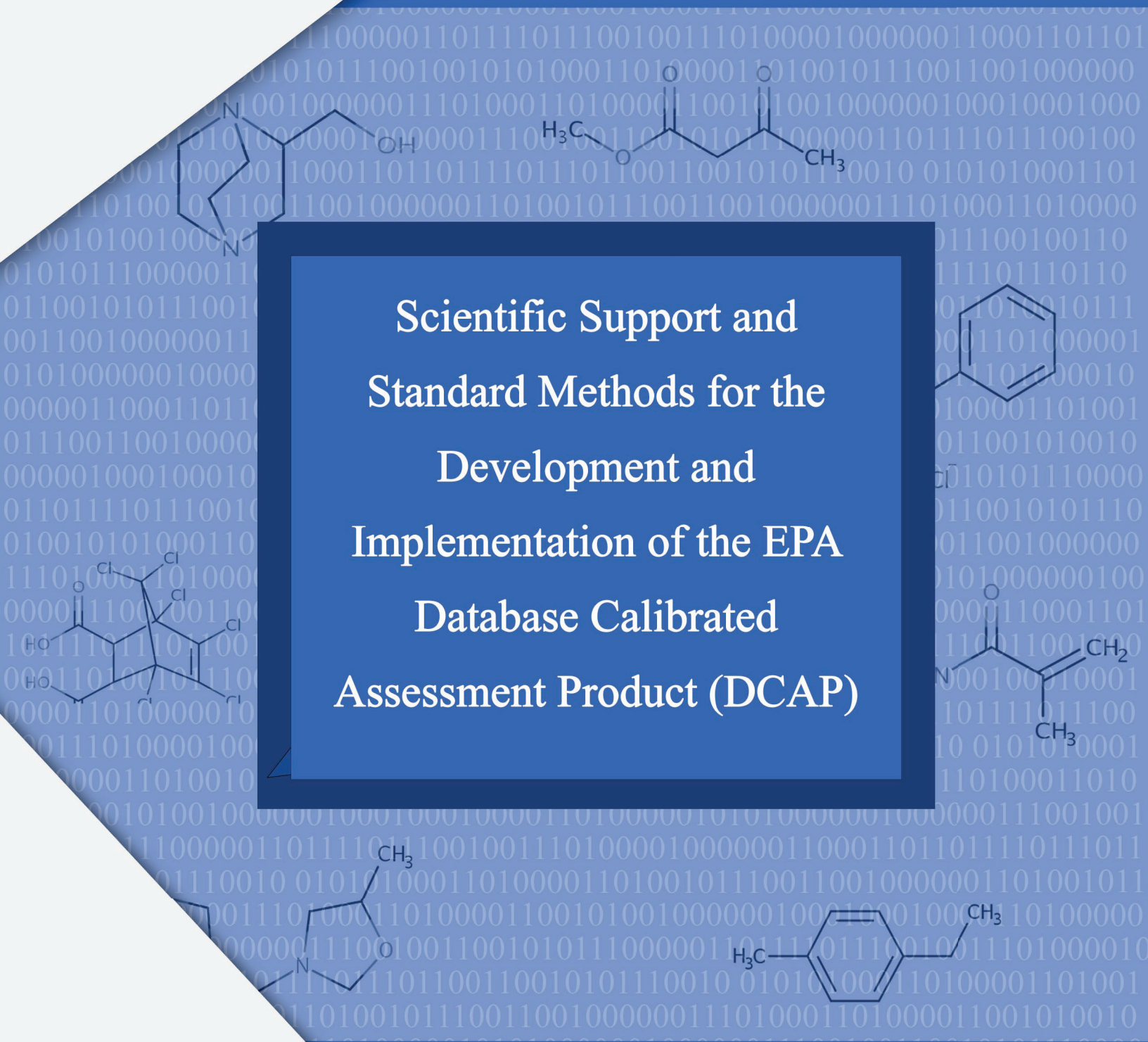

Scientific Support and Standard Methods for the Development and Implementation of the EPA Database Calibrated Assessment Product (DCAP)

Office of Research and Development
Center for Computational Toxicology and Exposure

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U.S. Environmental Protection Agency

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ABBREVIATIONS

ATSDR	Agency for Toxic Substances and Disease Registry
AUTH	Authoritative
BCTD	Biomolecular and Computational Toxicology Division
BMD	Benchmark Dose
BMDL	Benchmark Dose Lower Confidence Limit
BOSC	Board of Scientific Counselors
BW	Body Weight
CAA	Clean Air Act
CASRN	Chemical Abstracts Service Registry Number
CCCB	Computational Chemistry and Cheminformatics Branch
CCED	Chemical Characterization and Exposure Division
CCTE	Center for Computational Toxicology and Exposure
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CF	Conversion Factor
CPDAT	Chemicals and Products Database
CPHEA	Center for Public Health and Environmental Assessment
cPOD	Calibrated Point-of-Departure
CTBB	Computational Toxicology and Bioinformatics Branch
CTV	Calibrated Toxicity Value
CWA	Clean Water Act
DB	Database
DCAP	Database-Calibrated Assessment Product
Dev	Developmental
DEQEB	Data Extraction and Quality Evaluation Branch
DRSV	Dose Response Summary Value
DSSTox	Distributed Structure-Searchable Toxicity Database
DTT	Division of Translational Toxicology
DTXCID	Distributed Structure-Searchable Toxicity Database (DSSTox) Compound Identifier
DTXSID	Distributed Structure-Searchable Toxicity Database (DSSTox) Substance Identifier
eBMD	Estimated Benchmark Dose
$eBMD_{HED}$	Estimated Benchmark Dose, Human Equivalent Dose
ECHA	European Chemicals Agency
ECUA	Effective Composite Uncertainty Adjustment
ECOTOX	ECOTOX Knowledgebase
EFSA	European Food Safety Authority
EPA	U.S. Environmental Protection Agency
ETAP	EPA Transcriptomic Assessment Product
ETTB	Experimental Toxicokinetics and Toxicodynamics Branch
GSD	Geometric Standard Deviation
HAWC	Health Assessment Workplace Collaborative
HEAST	Health Effects Assessment Summary Tables
HED	Human Equivalent Dose
HHTV	Human Health Toxicity Value
HPVIS	High Production Volume Information System
ID	Identifier
InChI	International Union of Pure and Applied Chemistry (IUPAC) International Chemical Identifier
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
ISA	Integrated Science Assessment

IUPAC	International Union of Pure and Applied Chemistry
JECFA	Joint Expert Committee on Food Additives of the World Health Organization
LEL	Lowest Effect Level
LOAEL	Lowest Observed Adverse Effect Level
LOEL	Lowest Observed Effect Level
MAD	Median Absolute Deviation
MMDB	Multimedia Monitoring Database
MRL	Minimum Risk Level
NAAQS	National Ambient Air Quality Standards
NEL	No Effect Level
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NITE	National Institute of Technology and Evaluation of Japan
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NTP	National Toxicology Program
OECA	Office of Enforcement and Compliance Assurance
OEHHA	California Office of Environmental Health Hazard Assessment (CAL OEHHA)
OM	Order of Magnitude
ORD	Office of Research and Development
OW	Office of Water
p_{calib}	Optimal Calibration Percentile
POD	Point-of-Departure
PPRTV	Provisional Peer Reviewed Toxicity Value
QA	Quality Assurance
QC	Quality Control
RCRA	Resource Conservation Recovery Act
Rep	Reproductive
RfD	Reference Dose
RMSD	Root Mean Squared Difference
RPAS	Research Planning and Accountability Section
RPIS	Research Planning and Implementation Staff
SCDCD	Scientific Computing and Data Curation Division
SDWA	Safe Drinking Water Act
SG	Study Group
TD	Toxicodynamic
TK	Toxicokinetic
ToxVal	Toxicity Values
ToxValDB	Toxicity Values Database
TSA	Technical Systems Audit
TSCA	Toxic Substances Control Act
UCL	Upper Confidence Limit
UF	Uncertainty Factor
US	United States
UVCB	Substances of unknown or variable composition, complex reaction products or biological materials
WHO	World Health Organization

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1. EXECUTIVE SUMMARY

The United States (US) population is potentially exposed to thousands of different chemicals through multiple sources and pathways. The US Environmental Protection Agency (EPA) and other regulatory agencies routinely assess whether certain chemical exposures can result in harmful health effects. If risks to human health are identified, the EPA (or others) may take action to manage or mitigate such risks. Human health assessments play a critical role in the decision-making process by identifying chemical exposure levels likely to be without appreciable risk of deleterious effects. Most current human health assessments involve expert interpretation of experimental animal toxicology and human epidemiological studies, selection of the critical effect for dose response analysis, and derivation of a toxicity value that reflects the underlying uncertainty in the data. Due to the time- and resource-intensive nature of this process, most of the chemicals with potential human exposure lack expert-derived human health assessments, even when sufficient data may be available to develop such assessments.

To address the lack of human health assessments for these chemicals, the EPA has developed the Database-Calibrated Assessment Product (DCAP). DCAP is a methods-based approach to develop oral, non-cancer human health assessments that builds on the published approach of Aurisano and colleagues (Aurisano et al. 2023). The DCAP process uses the EPA-managed Toxicity Values Database (ToxValDB) that contains dose response summary values (DRSVs) from *in vivo* toxicity studies [*e.g.,* no observed adverse effect level (NOAEL), lowest observed adverse effect level (LOAEL), benchmark dose lower confidence limit (BMDL)]. The DRSVs from oral *in vivo* toxicity studies are converted into chronic, human equivalent estimated benchmark dose values ($eBMD_{HED}$) using conversion factors (CFs) derived from historical data with associated uncertainty based on guidance from the World Health Organization International Programme on Chemical Safety (WHO/IPCS) (WHO 2018). The conversion process adjusts for differences in the type of DRSV, study duration, study type, species, and toxicological effect. Following the conversion, a lognormal distribution of $eBMD_{HED}$ values is estimated for each chemical in the database. A subset of the chemicals that have non-cancer human health assessments from authoritative sources [*e.g.,* Agency for Toxic Substances and Disease Registry Minimum Risk Levels (ATSDR MRL), EPA Integrated Risk Information System (IRIS), EPA Provisional Peer Reviewed Toxicity Values (PPRTV), Health Canada] are used to identify the calibration percentile (p_{calib}) in the distribution of $eBMD_{HED}$ values that demonstrates the best concordance with the expert-selected points of departure (POD) used in the derivation of the associated toxicity values. The calibration percentile, p_{calib}, is applied to the $eBMD_{HED}$ distribution of the remaining chemicals that have *in vivo* toxicity studies but lack human health assessments. The combined uncertainty in the conversion and calibration processes are used to estimate the lower uncertainty limit of the value associated with the calibrated percentile, p_{calib}, in the $eBMD_{HED}$ distribution to provide a calibrated POD (cPOD). To derive the calibrated toxicity value (CTV), the

cPOD is divided by additional uncertainty factors (UF) that are not included in the calculation of the cPOD. The CTV is defined as an estimate of a daily oral dose to the human population that is likely to be without appreciable risk of adverse non-cancer health effects over a lifetime.

Evaluation of the DCAP process demonstrates that the median root mean squared deviation (RMSD) measuring concordance between the calibrated percentile from the distribution of $eBMD_{HED}$ values and the $eBMD_{HED}$ corresponding to the expert-selected critical effect is 0.614 with lower 5th and upper 95th percentiles of 0.504 and 0.701, respectively. The median and lower 5th percentile of the RMSD are similar to the reported range of interstudy standard deviation estimates of LOAEL values from multiple repeat dose studies for systemic toxicity (Pham et al. 2020). The similarity in the median and lower 5th percentile of the RMSD distribution with the range of RMSE values estimating interstudy variability of LOAEL values suggests that interstudy variability may comprise a substantial portion of the error associated with the calibration process. In addition to the calibration, a comparison of CTV values with expert-derived reference doses (RfD) from EPA assessments indicates a median absolute ratio of 7.9 $\pm$ 5.5 [$\pm$ median absolute deviation (MAD)]. A total of 87% of CTVs are lower than the corresponding RfD from the EPA assessments (*i.e.,* conservative from a human health protection standpoint). The conservatism in the CTV values is primarily due to the incorporation of a larger composite uncertainty. A comparison of the effective composite uncertainty adjustment (ECUA) from the CTVs and the composite UF values from EPA's IRIS and PPRTV assessments indicates that the median composite uncertainty is approximately two-fold higher in DCAP-derived CTVs. Consideration of the relative contributions of the uncertainties in DCAP shows that the five sources of uncertainty considered in traditional human health assessment contribute approximately 50 – 63% of the adjustment expressed on the log-scale. The remaining uncertainty is from other sources associated with the DCAP process (*e.g.,* uncertainty in the calibration).

Demonstration of the DCAP process is illustrated using a set of 8 chemicals that were selected based on differences in the number of studies associated with a chemical as well as a chemical without a defined structure or with unknown or variable composition, complex reaction products, or biological materials (UVCB).[1] Each of the 8 DCAP documents are generated as a portable document format (PDF) file using a computationally automated process that is both scalable and rapidly executable. Implementation of DCAP is projected to occur with the release of an estimated 1,100 assessments in batches over the course of a one-year period. Chemicals that have an existing expert-derived human health assessment from select authoritative sources are not eligible for issuing a DCAP. The phased approach allows for manual quality control (QC) of the relevant records in ToxValDB, a quality assurance (QA) audit of the DCAP process, and the development of the infrastructure to accommodate the new human health assessment product. Depending on available

[1] UVCB is a term used under the Toxic Substances Control Act (TSCA) for a class of chemical substances that cannot be represented by unique structures and molecular formulas.

resources, ToxValDB may be updated with newly available information on a periodic basis. As ToxValDB is updated, a new DCAP may be issued for a new chemical meeting the information requirements while an existing DCAP may be updated if new data are available. If an expert-derived, authoritative human health assessment is released on a chemical with a DCAP, the DCAP will be retired and archived.

The overall conclusions from the DCAP development, evaluation, and demonstration generally support its implementation as an ORD human health assessment product. The potential limitations of DCAP include the calculation of a cPOD that is not associated with a specific hazard or adverse effect as well as the lack of a formal confidence evaluation on the studies underpinning the distribution of $eBMD_{HED}$ values. In addition, the methods used to estimate some of the uncertainties (*i.e.,* UF_S, uncertainty in extrapolating from shorter-duration studies to chronic duration; UF_L, uncertainty in extrapolating from a LOAEL to a NOAEL; and UF_A, uncertainty in extrapolating from an animal to a human) rely on WHO/IPCS guidance and analysis of historical data that is different from standard EPA practice. Despite these limitations, implementation of DCAP is supported based on the performance of the method in approximating PODs from expert-derived human health assessments and the relative level of human health protection by the CTV values when compared to traditional EPA human health assessments. DCAP implementation is further supported by the ability to provide timely, transparent, and scalable human health assessments for chemicals with *in vivo* toxicity studies, but without expert-derived authoritative toxicity values. If implemented, DCAP would nearly triple the number of human health assessments available for chemicals with potential human exposure in support of EPA's mission of protecting human health and the environment.

2. BACKGROUND

2.1. CHEMICAL EXPOSURE LANDSCAPE

Chemicals are used, consumed, and released into the environment in nearly all sectors of the United States (US) economy. While there is no complete characterization of human chemical exposures from these sources, a cross-sectional analysis of selected studies and databases can provide surrogates of potential exposure through different routes or pathways. For chemicals that are present in the US economy, the Toxic Substances Control Act (TSCA) inventory provides a snapshot of all chemicals manufactured, processed, or imported in the country for specified uses under TSCA. In 2024, the TSCA inventory[2] contained 86,770 chemicals, of which 42,377 are considered commercially active. While the 28,903[3] chemicals that are on the non-confidential active TSCA inventory indicate their presence in the US economy, even this substantial set of chemicals does not fully represent the breadth of chemicals in commerce because the non-confidential active inventory does not include confidential chemicals, unintentionally produced materials (*e.g.,* unreacted intermediates, by-products, or degradation products), or manufactured chemicals that are excluded because they do not meet the thresholds required for registration.

In addition to chemicals regulated under TSCA, the EPA Chemicals and Products Database (CPDat)[4] provides quantitative and qualitative information on chemical ingredients in consumer products based on material safety data sheets and ingredients lists (Dionisio et al. 2018). The 34,937 chemicals included in CPDat provide an indication of potential indoor exposures or consumer use from commercial products. Similarly, the EPA Multimedia Monitoring Database (MMDB)[5] compiles harmonized public monitoring data from approximately 20 sources (Isaacs et al. 2022). The 3,271 chemicals included in the MMDB indicate their presence in different environmental and indoor media, human biofluids, and in wildlife tissues and other food sources. For lists of representative chemicals in select waste streams, databases of chemicals identified in biosolids[6] and produced water[7] (Danforth et al. 2020) provide information on substances in human waste and by-products derived from oil and gas extraction. The two lists provide a combined 1,799 chemicals. Finally, a literature review of multiple biomonitoring studies compiled a list of endogenous and exogenous

[2] US EPA TSCA Inventory: https://www.epa.gov/tsca-inventory
[3] TSCA Non-Confidential Active Inventory (February 2024): https://comptox.epa.gov/dashboard/chemical-lists/TSCA_ACTIVE_NCTI_0224
[4] Chemical and Products Database: https://comptox.epa.gov/dashboard/chemical-lists/CPDATv2
[5] Multimedia Monitoring Database: https://comptox.epa.gov/dashboard/chemical-lists/MMDBV1
[6] Biosolids: https://comptox.epa.gov/dashboard/chemical-lists/BIOSOLIDS2022
[7] Produced water exists in subsurface formations and is brought to the surface during oil and gas production: https://comptox.epa.gov/dashboard/chemical-lists/PRODWATER

chemicals that comprise the blood exposome (Barupal and Fiehn 2019). Filtering the chemicals identified in the literature review for only those on the TSCA inventory provides a list of 4,896 exogenous chemicals that have been identified in human blood.[8] Taken together, these lists represent a total of 53,550 unique chemicals present in different indoor and outdoor media, consumer products, waste streams, and the US economy to which humans may be exposed (**Fig. 2-1**).[9]

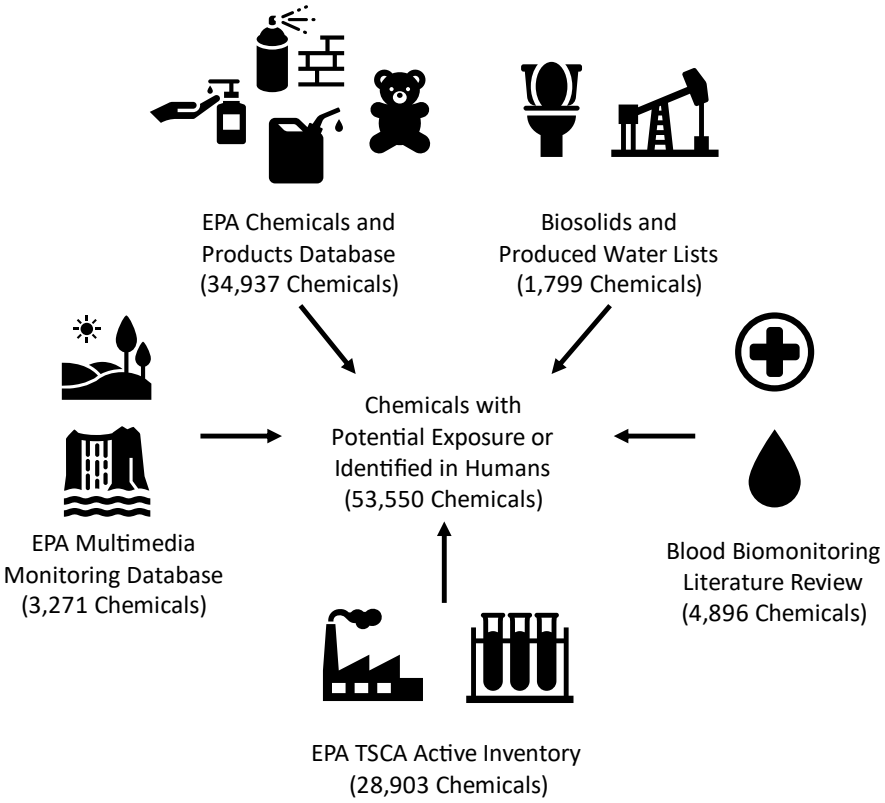


Figure 2-1. Chemicals identified in different indoor and outdoor media, consumer products, waste streams, human blood, and the US economy. The chemicals represent a cross-sectional database survey of those chemicals to which the US population may be exposed or that have been identified in the human body.

[8] TSCA subset of the blood exposome: https://comptox.epa.gov/dashboard/chemical-lists/BLOODTSCA. The TSCA subset of the blood exposome was used to represent the exogenous chemicals among those detected.
[9] The combined number provides an illustration of the lower bound on the number of chemicals to which the US population may be potentially exposed since the lists do not include all exposure pathways and each list is incomplete in the exposure pathway it represents (*e.g.,* the TSCA active non-confidential inventory does not include confidential substances).

2.2. HUMAN HEALTH ASSESSMENT LANDSCAPE

Human health assessments are typically developed to identify chemical exposure levels likely to be without appreciable risk of deleterious effects during an individual's lifetime or for shorter duration exposures (*e.g.,* subchronic). These assessments inform a broad range of decisions at the federal, state, and local level. To provide a picture of the human health assessment landscape, the availability of human health assessments from EPA and the Agency for Toxic Substances and Disease Registry (ATSDR) were tallied across the sets of chemicals described in Section 2.1 to which the US population may be exposed or that have been identified in the human body. These data are depicted in **Figure 2-2**. Across all the sets of chemicals, the maximum percentage of chemicals with an existing human health assessment is 20% of those identified in biosolids. For chemicals in produced water, approximately 13% have human health assessments, while only 9% of chemicals identified in human blood have available assessments. Among chemicals on the non-confidential TSCA active inventory, fewer than 2% of chemicals have human health assessments. Based on this comparison, there are a

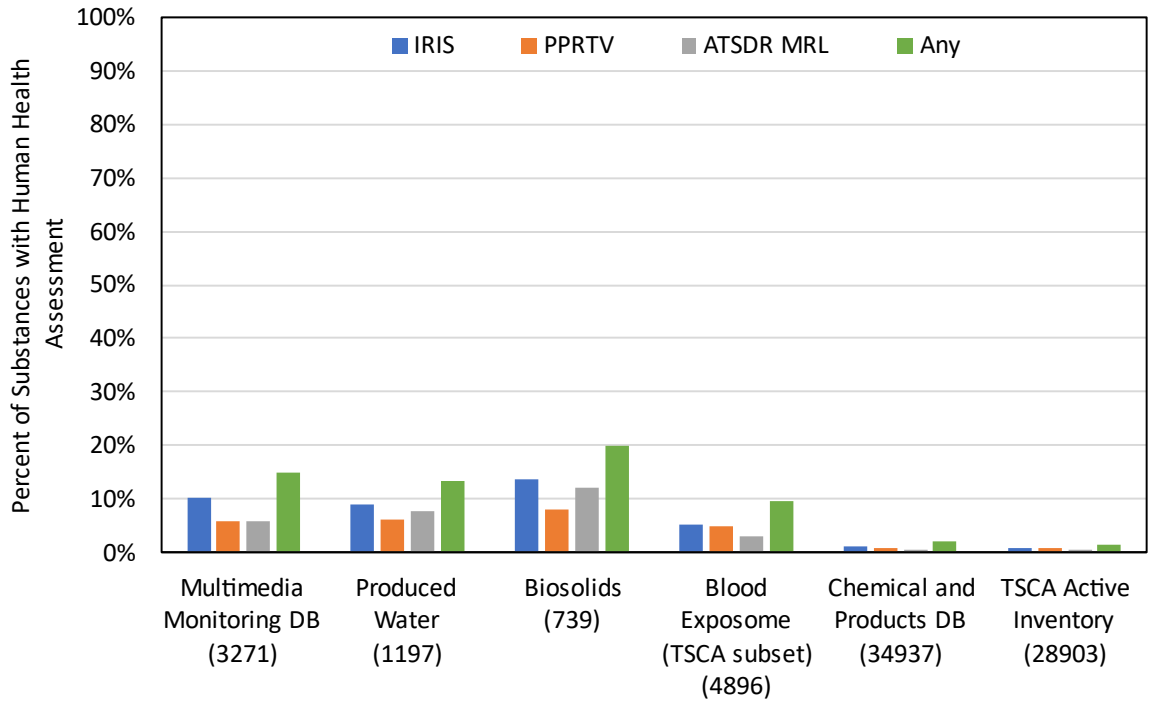


Figure 2-2. Bar graph depicting the percentage of chemicals with human health assessments from US federal agencies across the chemical sets to which the US population may be exposed or have been identified in the human body. The percentages of chemicals with human health assessments were calculated based on the overlap with chemicals with non-cancer human health assessments in the EPA Integrated Risk Information System (IRIS) database, the EPA Provisional Peer Reviewed Toxicity Values (PPRTV), and the Agency for Toxic Substances and Disease Registry (ATSDR) Minimum Risk Levels (MRL). The 'Any' category is the union of unique chemicals across the various assessment types. The total percentages of chemicals across assessment types may not equal the total percentage in 'Any' given that chemicals may have multiple different assessments (*e.g.,* a chemical may have an IRIS RfD and ATSDR MRL). The total number of chemicals in a list is shown in parentheses.

substantial number of chemicals to which humans may be exposed that do not have human health assessments.

2.3. DEVELOPMENT OF THE EPA DATABASE-CALIBRATED ASSESSMENT PRODUCT (DCAP)

2.3.1. EXISTING PORTFOLIO OF ORD HUMAN HEALTH ASSESSMENT PRODUCTS

Over the last four decades, the EPA Office of Research and Development (ORD) has developed and refined a portfolio of human health assessment products. The assessment products are tailored to different intended decision contexts, the size of the relevant evidence base, and the approach taken to develop the assessment (**Table 2-1**). Among these products, the Integrated Science Assessments (ISAs)[10] are developed for the criteria air pollutants under the National Ambient Air Quality Standards (NAAQS)[11]. The ISAs are founded on a large and complex evidence base and require multiple years to develop. The second product in the portfolio is the Integrated Risk Information System (IRIS)[12] assessments, which are intended for broad application across national and site-specific decisions that include those under the Clean Air Act (CAA), Safe Drinking Water Act (SDWA), Clean Water Act (CWA), Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), Resource Conservation Recovery Act (RCRA), and others. IRIS assessments are also developed using a relatively large evidence base and may involve complex modeling and analyses of available data. Similar to ISAs, IRIS assessments require multiple years to complete. The third product in the portfolio is the Provisional Peer-Reviewed Toxicity Values (PPRTVs[13]), which are developed for site-specific clean-up decisions under CERCLA. PPRTVs usually have a moderate- to small-sized evidence base and do not typically include the more complex modeling and data analytics inherent to IRIS assessments. In some cases, PPRTVs are developed using expert-driven read-across wherein dose-response data are adopted as a surrogate from a closely related analogue chemical. Due to the smaller evidence base and less complex analyses, PPRTV assessments usually take approximately 18 months to develop. The fourth product is the Human Health Toxicity Values (HHTVs). HHTVs are a relatively new assessment product that may include a broad range of evidence bases, from large to relatively small. Further, HHTVs were developed to meet specific needs of EPA program and regional offices for targeted decision-making contexts across different acts/authorities. For example, two of the three HHTVs that have been released to date were developed in response to requests by the EPA Office of Enforcement and Compliance Assurance (OECA) to inform site-specific decisions under the SDWA. The third HHTV that was released was developed to support multiple EPA

[10] Information on EPA Integrated Science Assessments may be accessed at: https://www.epa.gov/isa
[11] Information on National Ambient Air Quality Standards may be accessed at: https://www.epa.gov/naaqs
[12] Information on the EPA Integrated Risk Information System may be accessed at: https://www.epa.gov/iris
[13] Information on the EPA Provisional Peer-Reviewed Toxicity Values may be accessed at: https://www.epa.gov/pprtv

Program Offices and Regions in decision-making associated with the chemical's presence in water and/or soil under diverse authorities (*e.g.,* SDWA, CWA, CERCLA). HHTV assessments can take months to years depending on the size of the evidence base. The final and most recent product in the portfolio, the EPA Transcriptomic Assessment Product (ETAP[14]), is intended for broad application across national and site-specific decisions. The ETAP is based on a defined study method and has a specific context-of-use for chemicals lacking any hazard and dose-response evidence applicable to the derivation of non-cancer toxicity values (EPA 2024a). Due to the streamlined experimental and assessment development process, the ETAP is targeted for completion in 9 months. The ISA, IRIS, PPRTV, and HHTV assessments are all developed through expert data collection, assembly, and interpretation of the evidence base, while the ETAP is a defined analysis method that is applied to a standardized short-term experimental animal study. The differences among the assessment products are important for meeting programmatic needs while maintaining a fit-for-purpose approach for protecting human health.

Table 2-1. Characteristics of EPA ORD's human health assessment products

Product Name	Intended Decision Context	Evidence Base	Relative Time to Develop	Approach
Integrated Science Assessments (ISAs)	Criteria Air Pollutants	Very Large	Long	Expert-Based
Integrated Risk Information System (IRIS)	National and Site Specific	Large	Long	Expert-Based
Provisional Peer Reviewed Toxicity Values (PPRTVs)	Superfund	Moderate - Small	Short	Expert-Based
Human Health Toxicity Values (HHTVs)	National and Site Specific	Variable	Short - Moderate	Expert-Based
EPA Transcriptomic Assessment Product (ETAP)	National and Site Specific	Single Standardized Study	Very Short	Method-Based

2.3.2. CHEMICALS WITH TOXICITY DATA THAT LACK HUMAN HEALTH ASSESSMENTS

Despite the availability of diverse human health assessment products within ORD, there remains a substantial difference between the number of chemicals that have traditional *in vivo* repeat-dose toxicity testing data and those that have toxicity values from human health assessments. Considering sets of chemicals to which the US population may be exposed or have been identified in the human body, the number of chemicals with *in vivo* repeat-dose toxicity testing studies and no human health assessment are provided in **Figure 2-3**. Across all sets of chemicals, the maximum number of chemicals with *in vivo* repeat-dose toxicity studies, but no human health assessment is in the EPA Chemical and Products Database with between 1,000 and 2,700 chemicals depending on the number of toxicity studies. A similar range of chemicals are present on the non-confidential TSCA

[14] For more information, visit the ETAP information page at: https://www.epa.gov/etap

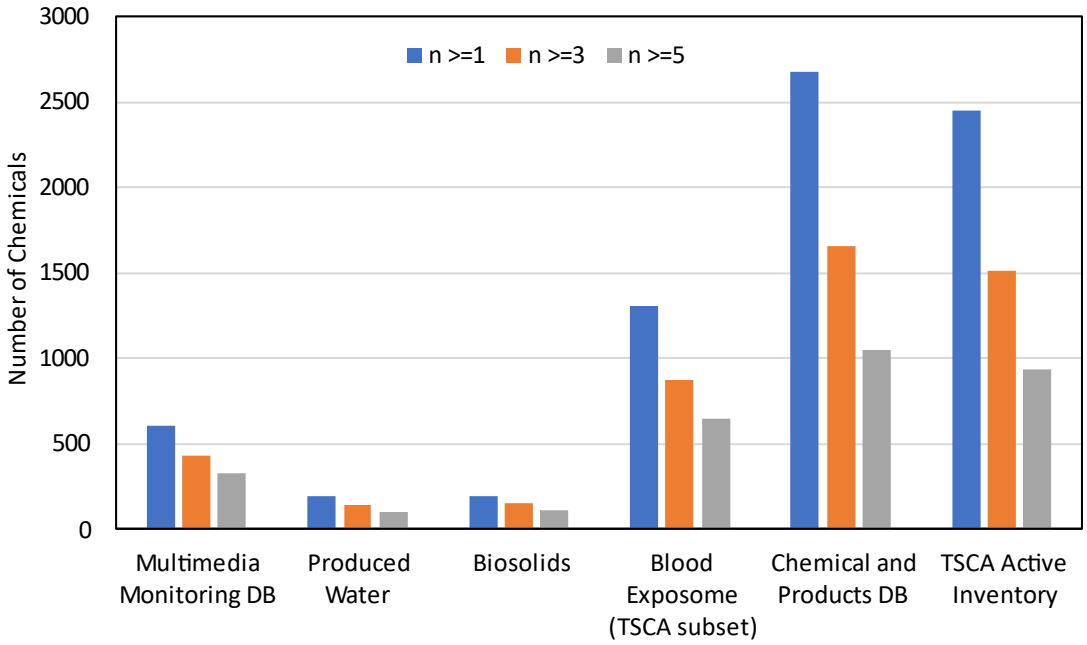


Figure 2-3. Bar graph depicting the number of chemicals with traditional oral repeat-dose systemic, developmental, or reproductive *in vivo* toxicity testing study and no human health assessments from US federal agencies across the chemical sets to which the US population may be exposed. The number of chemicals with repeat-dose systemic, developmental, or reproductive *in vivo* toxicity studies were obtained from the EPA Toxicity Values database (ToxValDB) (version 9.6.0). The repeat-dose *in vivo* toxicity studies were curated from a variety of sources (see Section 3) and required to have repeat-dose exposures of at least 14-days in length. The blue, orange, and gray bars represent the number of chemicals with n >1, n >3, and n >5 study groups, respectively. Study groups are defined in Section 3.

active inventory and between 650 and 1,300 chemicals identified in human blood have *in vivo* repeat-dose toxicity studies but no human health assessment. Based on these comparisons, there remains a substantial number of chemicals to which humans are potentially exposed that have available *in vivo* repeat-dose toxicity studies, but do not have human health assessments.

One of the reasons there are significant numbers of chemicals with *in vivo* repeat-dose toxicity data, but no human health assessment, is that it takes substantial time and resources to develop and complete an expert-derived human health assessment. To develop an assessment, significant resources are required to identify and assemble the various sources of experimental animal toxicology and human epidemiological studies, systematically examine the studies for relevance and quality, identify the landscape of potential adverse effects, and perform dose response analyses. Based on considerations such as strength of evidence and quantitative sensitivity, the

critical effect and point-of-departure (POD)[15] are selected and then divided by a number of uncertainty factors (UF) that together address important experimental, variability, and extrapolation considerations to obtain the toxicity value (EPA 2002). The resulting study review, hazard and dose-response assessment, reference value derivation, and assessment conclusions are summarized, undergo requisite review, and are published. Each step in this process is time and resource intensive, such that the development of expert-derived human health assessments typically takes at least 18 months for a PPRTV and multiple years for an ISA or IRIS assessment.

2.3.3. DEVELOPMENT OF THE EPA DATABASE-CALIBRATED ASSESSMENT PRODUCT (DCAP)

To address the gap in the human health assessment of these chemicals, the EPA is proposing to develop the Database-Calibrated Assessment Product (DCAP) as a new addition to the ORD assessment portfolio. The DCAP uses a method-based approach to develop oral, non-cancer human health assessments that provide calibrated toxicity values (CTVs). The CTV is defined as an estimate of a daily oral dose to the human population that is likely to be without appreciable risk of adverse non-cancer health effects over a lifetime. The DCAP is intended to be applied to substances with existing, publicly accessible *in vivo* repeat-dose toxicity studies, but lacking expert-derived human health assessments from select authoritative sources. DCAPs may be updated to incorporate new data that might impact the CTV, or retired if an expert-derived human health assessment is published from an authoritative source.

The DCAP process builds on previously published methods (Aurisano et al. 2023; Chiu and Slob 2015; WHO 2018) and consists of two main parts: 1) data consolidation and preparation (described further in Section 3); and 2) data conversion, calibration, and uncertainty characterization to derive a CTV (**Fig. 2-4**) (described further in Section 4). In the data consolidation and preparation step, toxicity testing data from select information sources are extracted, imported into ToxValDB, and evaluated for fidelity to the corresponding source documents. The ToxValDB records are filtered to retain those that are relevant to DCAP and select data fields are standardized to ensure consistency in downstream data processing. The dose response summary values [DRSVs; *e.g.,* no observed adverse effect level (NOAEL), lowest observed adverse effect level (LOAEL), benchmark dose lower confidence limit (BMDL)] in the ToxValDB records are converted to chronic, estimated human equivalent benchmark dose ($eBMD_{HED}$) values using conversion factors derived from historical data based on World Health Organization International Programme on Chemical Safety (WHO/IPCS) guidance (WHO 2018). The distribution of $eBMD_{HED}$ values is calibrated to PODs associated with

[15] In human health risk assessment practice, a POD represents the dose-response point that marks the beginning of a low-dose extrapolation. This point can be the lower bound on dose for an estimated incidence or a change in response level from a dose-response model (*e.g.,* Benchmark Dose; BMD), or a No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect Level (LOAEL) for an observed incidence or change in level of response (taken from EPA IRIS glossary).

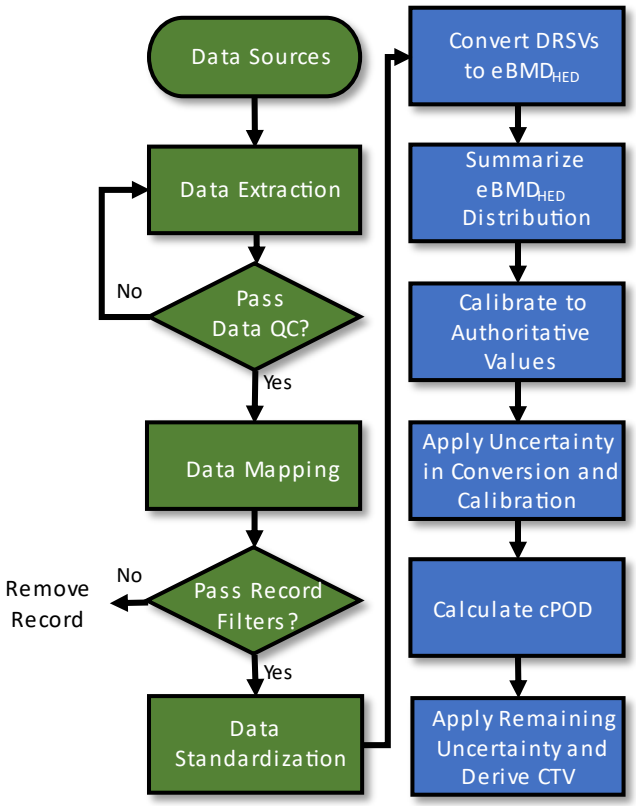


Figure 2-4. Overview flowchart depicting the two main components of the DCAP process: data consolidation and preparation (green); and data conversion, calibration, and uncertainty characterization to derive a CTV (blue). Each component consists of multiple steps that are required to go from a diverse collection of toxicity studies to a CTV and assessment for each chemical. The multiple steps involved in the data consolidation and preparation are outlined in Section 3, while the steps involved in data conversion, calibration, and uncertainty characterization to derive a CTV are outlined in Section 4.

expert-selected, critical effects from authoritative human health assessments. The calibration process is used to calculate a calibrated POD (cPOD)[16] and includes integration of quantitative uncertainty associated with animal-to-human (UF_A), subchronic-to-chronic duration (UF_S), and LOAEL-to-NOAEL (UF_L) extrapolation as required by the available data as well as uncertainty that is specific to the DCAP process. Additional uncertainty associated with intraindividual variability in human population(s) (UF_H) and the available chemical-specific database (UF_D) is applied to the cPOD to derive a CTV. The results from the data compilation, calibration, and CTV derivation are compiled and reported in a standard DCAP template using an automated computerized process. Due to the standardized computational methodology, the DCAP includes a streamlined review process that is intended to facilitate the development and release of the human health assessments.

[16]In this document, the cPOD is defined as the lower uncertainty limit of the value associated with the calibrated percentile of a distribution of chronic duration eBMD$_{HED}$ values derived from multiple human health relevant studies. The percentile has been calibrated to PODs for critical effects from select authoritative sources.

2.4. BOARD OF SCIENTIFIC COUNSELORS (BOSC) SCIENTIFIC REVIEW OF DCAP DEVELOPMENT AND IMPLEMENTATION

The EPA Board of Scientific Counselors (BOSC) is requested to perform a scientific peer-review of the development and implementation of the proposed DCAP. To support the peer review, the document is organized to provide a detailed understanding of the DCAP method, characterization of the uncertainties incorporated into the cPOD and CTV, comparison of the CTV values with reference values from other EPA human health assessments, demonstration of the DCAP method for a set of select chemicals, and planned implementation of DCAP as a new ORD human health assessment.

3. DATA CONSOLIDATION AND PREPARATION

3.1. TOXICITY VALUES DATABASE (TOXVALDB)

The EPA ToxValDB is the main data source in the development of the DCAP. The EPA ToxValDB is a resource that was designed to store, standardize, and make accessible a broad range of publicly available toxicity information compiled from over 40 public sources. ToxValDB contains quantitative information on dose-effect/health outcome linkages from *in vivo* studies, including DRSVs (*e.g.,* NOAEL, LOAEL, BMDL) derived from published sources, as well as reference values issued by authoritative sources [*e.g.,* reference doses (RfDs)]. In addition to summary dose-response information, the database contains study descriptor and metadata when provided by the source on: 1) exposure route, duration, and identity of test material; 2) the generation, lifestage, and/or age of the animal(s); 3) biological effect and/or phenotypic health outcome; and 4) links to the underlying source material, whether a primary article, reference document, or information derived from other curated databases. The current version of ToxValDB (version 9.6.0, accessed December 2024) and associated documentation is available for download.[17]

3.1.1. DATA EXTRACTION

The data extraction process for ToxValDB is source dependent. Because each source contains different fields and uses different terminology, a custom database table is developed for each source in the ToxVal Source DB (**Fig. 3-1**). The source documents are collected and placed in the CCTE Clowder repository (an open-source, cloud-based file management system[18]) for future reference and linked to records in source database tables. Structured sources, encompassing data already organized into a machine-readable format, are programmatically extracted. Unstructured sources, encompassing long-form text documents such as published manuscripts, data evaluation records, and health assessment documents, are manually curated by trained staff. The curation team determines the required information to capture from each source, and the relevant data are extracted into a standard data-entry template of ToxValDB fields.

An important step in the import process is the deduplication of records. Duplicates may be present due to additional metadata fields reported by the source which are stored in the custom database table for reference, but not used in ToxValDB. To accomplish deduplication of records,

[17] The ToxValDB data are available on the CompTox data download website: https://www.epa.gov/comptox-tools/downloadable-computational-toxicology-data
[18] Information on Clowder can be found at: https://clowderframework.org

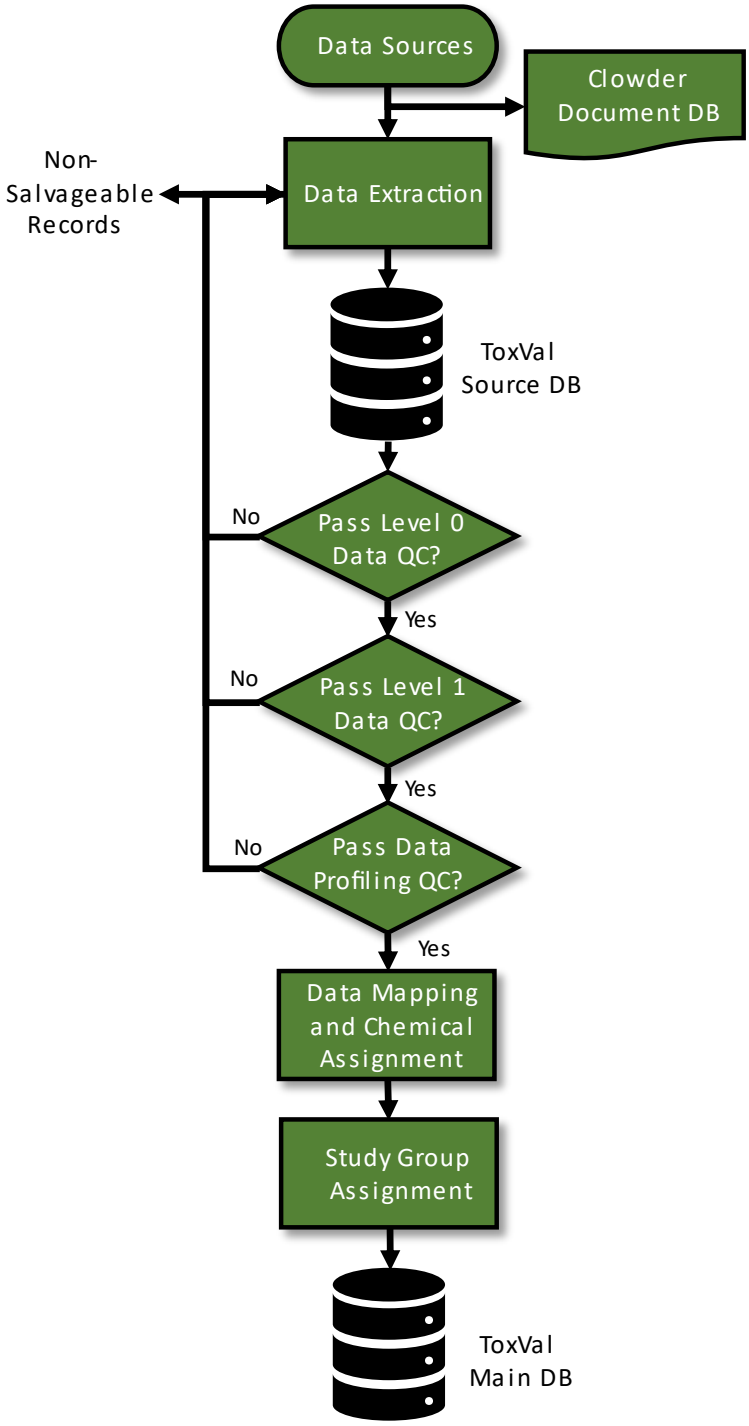


Figure 3-1. Detailed flowchart of the data extraction, QC, data mapping, and study group assignment process for developing ToxValDB.

records are grouped by ToxValDB specific fields (*e.g.,* species, sex, study duration, DRSV) to determine duplicates in these specific fields and merged into a single record. All non-ToxValDB field original values for duplicate records are maintained as a list separated by a unique delimiter denoting

the merged (*i.e.,* de-duplicated) record. The merged record is what is transferred to the ToxVal Main DB.

3.1.2. DATA QUALITY CONTROL

After importing into the ToxVal Source DB, the data undergo an initial quality control (QC) evaluation (**Fig. 3-1**). The extent of additional QC required is based on whether data are extracted manually from an unstructured data source or extracted programmatically from a structured data source. Documentation of source-level QC prior to ToxValDB import is also considered. Source-level QC has two tiers: Level 0 and Level 1. Level 0 QC entails a manual evaluation of all sources (regardless of extraction approach) to check for any systematic errors in the data importation step and to ensure the correct information is represented in each data or metadata field of ToxValDB. QC reviewers are provided the full source table and a summary of unique values in each table field. Reviewers assess whether the field values are appropriate and whether the records contain the minimum information to be considered for inclusion in ToxValDB. For any sources that fail Level 0 QC, the source import process is reviewed and revised until all fields containing information from the source are correctly displayed in ToxValDB.

Level 1 QC entails an evaluation of extraction accuracy by comparing ToxValDB records to the source where data are extracted. The goal is to ensure records in ToxValDB are accurate representations of the source data. When errors are identified during Level 1 QC, the record is corrected and adjustments made to the full set of source records based on the error type (*e.g.,* systematic, semantic). Level 1 QC of the data importation typically involves a subsample of the full source, where the number of records reviewed is based on the data extraction method. For programmatically extracted sources, a random subsample of 100 records is reviewed in an export file from each source. The assumption in reviewing a subset of records is that systematic errors introduced by the programmatic extraction and processing would be identified in Level 0 QC, and that a subsample is representative of the whole. When errors are identified, the extraction and import code is revised, and the data are re-imported and refreshed. Level 1 QC continues until all 100 subsampled records pass review without error.

For manually extracted sources within ToxValDB, a minimum of 20% of records are manually and independently reviewed for accuracy under Level 1 QC. For selected records, QC is performed to evaluate the accuracy of ToxValDB records with the original document(s). The source record from ToxVal Source DB is displayed alongside the extraction document, and a reviewer confirms that the values in the record match those in the document. When errors are identified during Level 1 QC, the record is corrected in ToxVal Source DB. An audit trail of QC actions is incorporated into the ToxVal Source DB and processed into the ToxVal Main DB. Finally, for data derived from ToxRefDB, QC is conducted prior to inclusion in the original databases and no additional Level 1 QC is required (Feshuk et al. 2023; Watford et al. 2019). Although Level 1 QC is typically performed on only a subsample of records for most sources within the main ToxValDB, Level 1 QC is performed on 100%

of the DCAP-relevant records utilized for calibration and the subset of example chemicals demonstrating application of the method.

Additional record-level QC-fail tags are set during the transfer of records from the ToxVal Source DB to the ToxVal Main DB. These additional QC-fail tags are field specific and include meta-information such as whether records are out of scope for ToxValDB (*e.g., in vitro* study), represent duplicates across sources, or include ambiguous toxicity units (*e.g.,* g/kg). Duplicates are present between sources when the results reference the same underlying reports or studies. This is resolved using a deduplication hierarchy, where tagged source records are set to "fail" status if they are present in another source. For example, because EPA IRIS superseded EPA Health Effects Assessment Summary Tables (HEAST), duplicate chemicals are prioritized from EPA IRIS and corresponding HEAST records are set to "fail". The basic criterion for the decision is having the same chemical records, but deduplication efforts also consider the reported DRSV or other fields where duplication of records can be identified.

In addition to Level 0 and Level 1 QC evaluation, a series of data profiling reports are generated on the complete database to identify records or fields for review that could be potentially erroneous. For example, a report of unique combinations of effect type, exposure route, and dose units is developed for consistency (*e.g.,* a record with an apparent mismatch of having an oral exposure route, but dose units in mg/m^3 would be evaluated against the source document for potential discrepancies). Reports are also generated to identify potential duplicate records and any records with a large numeric spread or deviation of DRSVs when grouped by chemical.

3.1.3. DATA MAPPING AND INITIAL STANDARDIZATION

Source data are imported into ToxValDB as reported in the original source. There is heterogeneity across sources for many terms, ranging from minor differences in spelling to variation in how terms are defined. To standardize terminology and facilitate comparisons across the database, ToxValDB maps source terms into a single common controlled vocabulary per field (*e.g.,* species, strain, units, study type) using dictionaries. Where possible, the dictionaries are developed using terms from a trusted source (*e.g.,* NIH National Center for Biotechnology Information for species scientific names; EPA sources for study types, units). Dictionaries are updated as new source terms are added to the database.

The study duration fields (*i.e.,* study duration value, study duration units, and study duration class) are combined into a single dictionary. Study duration value is a numeric field that does not allow for text or special characters. When duration is not reported, the value field is populated with "-999". For developmental exposure durations that are reported in the source documents as the period of exposure, the number of days is calculated and reported as the study duration value and study duration units. To capture that the exposure includes a developmental study design, "developmental" is appended within parentheses to the study duration class. Study duration class is based on the length of exposure (in commonly used experimental animals such as rodents), where

acute is defined as ≤1 day, short-term as >1-30 days (1-4 weeks), subchronic as 31-90 days (>4-13 weeks, >1-3 months), and chronic as ≥ 91 days (>13 weeks, >3 months, >0.25 years) (EPA 2002).

DRSVs as reported by the source are converted to a standard unit where possible. For oral exposure routes, units are standardized to mg per kg body weight per day (reported as mg/kg-day). For inhalation exposures, units are standardized to mg per cubic meter of air (reported as mg/m^3). For records with units not already reported as mg/kg-day, the standardizations follow a three-step process. First, the units dictionary is used to standardize synonymous terms to "ppm" (*e.g.,* "mg/kg diet", "ppm in food", "ppm air"). Next, the unit conversions dictionary is used to convert relevant units to "ppm" (*e.g.,* "mg/g diet" is multiplied by 1000 to get "ppm", L/m^3 is multiplied by 0.001 to get "ppm"). In the last step, "ppm" is converted to "mg/kg-day" for oral exposure routes or to "mg/m^3" for inhalation exposure routes. For oral exposure, a series of species and duration-specific standard conversion factors for diet and drinking water exposure methods are applied. The conversion factors are obtained from EPA recommendations for biological values for use in risk assessment (EPA 1988). For inhalation exposure routes, "ppm" is multiplied by molecular weight and the constant 0.0409, which assumes a pressure of 1 atmosphere and temperature of 25 degrees Celsius. All records with unconvertible or unclear units are QC tagged and excluded.

3.1.4. CHEMICAL SUBSTANCE ASSIGNMENT

To assign the chemical(s) tested in the source to a specific chemical substance, the extracted chemical name and/or Chemical Abstract Service Registry Number (CASRN) are cross referenced with content contained within the Distributed Structure-Searchable Toxicity (DSSTox) database (Grulke et al. 2019) to obtain a DSSTox substance identifier (DTXSID), an identifier unique to each chemical substance in DSSTox. For any chemicals not mapped to existing records in the DSSTox database, new registrations are performed. Each DTXSID is linked to a unique active CASRN (or assigned NOCAS if no CASRN is available), a single preferred chemical name, and other systematic names and synonyms. Mapping to unique chemical substance identifiers enables the toxicity data across multiple sources to be linked to the specific tested substance. For chemical substances with associated chemical structures, the DTXSID is also associated with a DSSTox compound identifier (DTXCID) and International Union of Pure and Applied Chemistry (IUPAC) International Chemical Identifier (InChI) string and InChIKey (Heller et al. 2015) as well as other structural representations, such as Simplified Molecular Input Line Entry System (SMILES) (Weininger 1988). For the remainder of this manuscript, specific chemicals will be referred to using DTXSID identifiers so that readers can view the associated chemicals on the CompTox Chemicals Dashboard.[19]

[19] The EPA CompTox Chemicals Dashboard is at: https://comptox.epa.gov/dashboard/

3.1.5. STUDY GROUP ASSIGNMENT

The records in ToxValDB contain data associated with five general categories: chemical characteristics, study characteristics, exposure characteristics, effect characteristics, and source characteristics (**Fig. 3-2**). The combination of data in these categories is referred to as a study group. The study groups are intended to link common records within a particular experimental study. For example, a particular subchronic *in vivo* toxicity study may have both a NOAEL and a LOAEL with each DRSV having a separate ToxValDB record. Similarly, a 28-day *in vivo* study may have multiple LEL values each with a different toxicological effect. Notably, a complete *in vivo* toxicity study may also have multiple study groups that are associated with it. Each sex, life stage, and generation are assigned different study groups such that a subchronic *in vivo* toxicity study that involves both male and female rats would have two study groups. Similarly, an *in vivo* developmental toxicity study would have separate study groups for the dam and fetus. The study group concept is used in ToxValDB to help differentiate toxicological responses among different sexes, life stages, and generations and accommodate studies that may not have a standard experimental design (*e.g.,* test chemical in only a single sex).

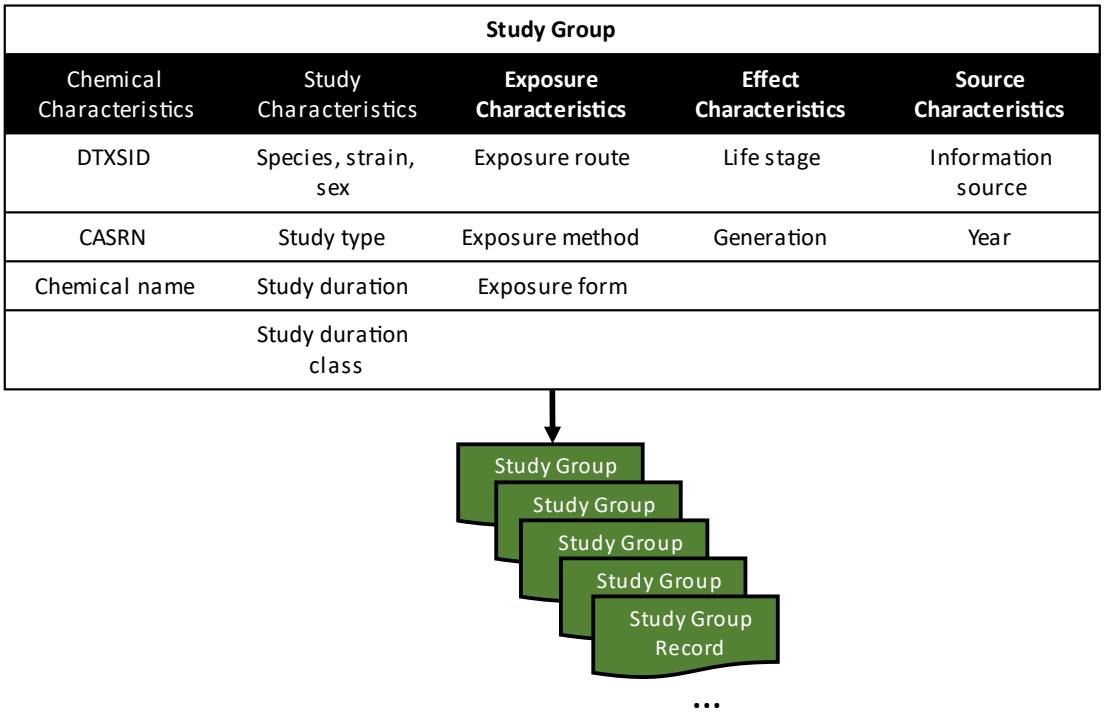


Figure 3-2. Assignment of ToxValDB records into study groups. ToxValDB records contain data associated with five general categories: chemical characteristics, study characteristics, exposure characteristics, effect characteristics, and source characteristics. The combination of data fields in these categories is referred to as a study group**.** Multiple ToxValDB records may be associated with a single study group.

3.2. TOXVALDB RECORD FILTERING

ToxValDB contains summary level data from diverse types of toxicity and toxicity-related studies, reference values from human health assessments, and exposure guidelines. Not all information in ToxValDB is relevant to, or meets the requirements for, inclusion in DCAP. The information must be filtered to obtain the relevant ToxValDB records (**Fig. 3-3**).

3.2.1. INFORMATION SOURCE FILTERING

For DCAP, only a select subset of EPA-managed and non-EPA-managed public sources from ToxValDB is utilized. The EPA-managed sources include the ECOTOX Knowledgebase (ECOTOX), the High Production Volume Information System (HPVIS), the Toxicity Reference Database (ToxRefDB), Health Assessment Workplace Collaborative (HAWC), Human Health Toxicity Values (HHTV), HEAST (including only chemicals distinct from IRIS), the Integrated Risk Information System (IRIS), and Provisional Peer-Reviewed Toxicity Values (PPRTV). The non-EPA-managed sources include the Agency for Toxic Substances and Disease Registry (ATSDR), California Office of Environmental Health Hazard Assessments (CAL OEHHA), the European Chemicals Agency (ECHA), the European Food Safety Authority's (EFSA) OpenFoodTox, the Health Assessment Workplace Collaborative Project (HAWC Project), Health Canada, Japan's National Institute of Technology and Evaluation (NITE), the National Toxicology Program (NTP), and the WHO Joint Expert Committee on Food Additives (JECFA). A list of ToxValDB information sources used in DCAP and associated access details are provided in the Appendix (Section 8.1).

3.2.2. STUDY CHARACTERISTICS FILTERING

The toxicity data collated within ToxValDB are derived from a variety of different study designs, exposure durations, and tested species, not all of which are relevant for the purposes of the DCAP. The initial data filtering step for DCAP constrains the included study characteristics to *in vivo* repeat dose toxicity studies in select mammalian species. The mammalian species included are mice, rats, rabbits, dogs, and humans. In addition to species, the reported study types and study duration classes in ToxValDB considered for DCAP include short-term, subchronic, chronic, repeat dose other, developmental, reproduction development, and clinical. Acute and short-duration studies with exposure durations of less than 14 days are excluded from the analysis.

3.2.3. EXPOSURE CHARACTERISTICS FILTERING

For the purposes of the DCAP, only the oral exposure route is considered. Oral exposure methods include food, drinking water, gavage, or capsule. The ToxValDB records associated with non-oral exposure routes (*e.g.,* inhalation) are excluded from the current analysis. Inhalation studies may be considered in future DCAP updates; however, adding the inhalation route would require the development of a parallel DCAP process. A recently published study has suggested that the addition of a DCAP for the inhalation route may be feasible (Aurisano et al. 2024).

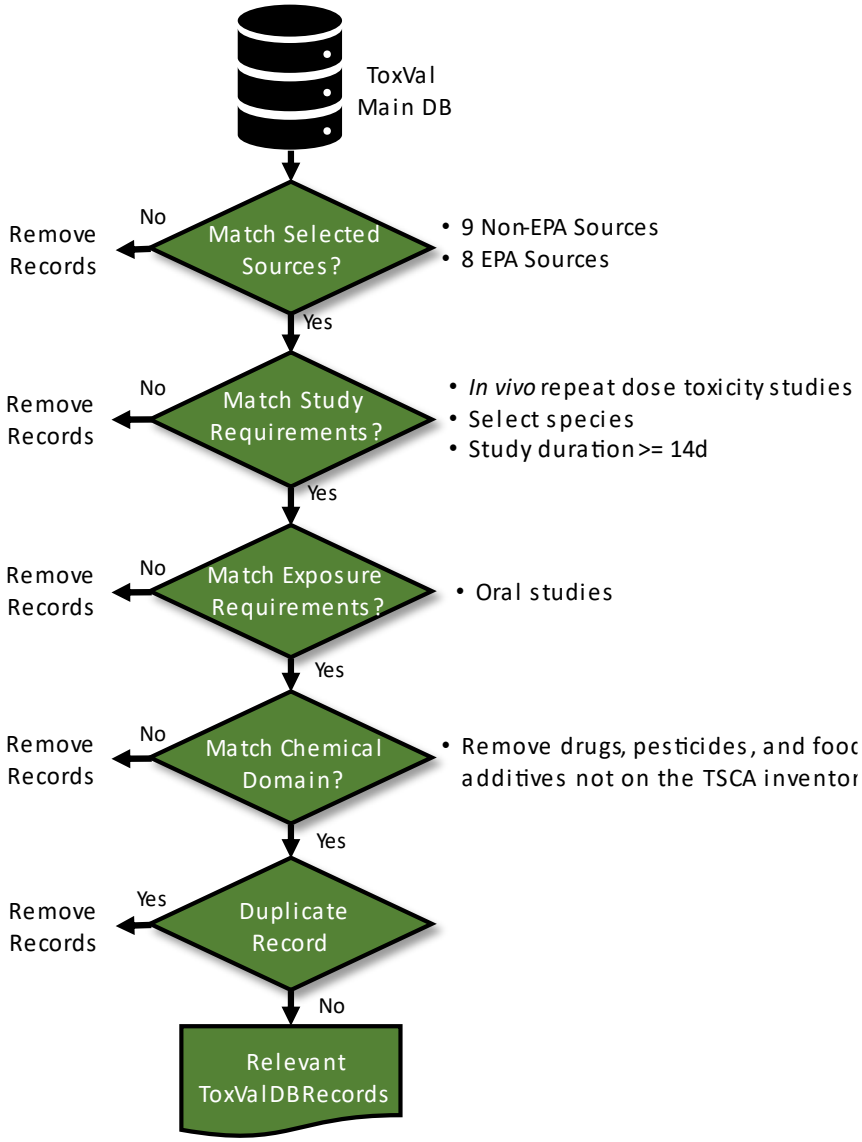


Figure 3-3. Detailed flowchart of the filtering process of ToxValDB records for DCAP. The filtering process is used to identify relevant ToxValDB records that meet the specified requirements for DCAP.

3.2.4. CHEMICAL DOMAIN FILTERING

Records in ToxValDB include chemicals across diverse structural and functional domains. The focus of DCAP is on chemicals of interest to EPA which do not currently have human health assessments. The approach excludes drugs, cosmetics, tobacco products, and food additives, which are regulated by the U.S. Food and Drug Administration (FDA), as well as pesticides, as pesticide registrants submit a defined set of toxicity studies to EPA to inform a risk assessment on those intended uses. However, some drugs, food additives, and pesticides have additional functional uses. For example, benzoic acid (DTXSID6020143) is listed as a pesticide but is also used in paints and

adhesives. Similarly, thiabendazole (DTXSID0021337) is listed as a drug by the FDA, but it is also used in paints, personal care products, and home cleaning products. The secondary uses of these chemicals are regulated under TSCA. The TSCA inventory excludes pesticides, drugs, foods and food additives, cosmetics, tobacco products, nuclear materials, and munitions unless they have multiple uses with at least one use being under TSCA. To limit the ToxValDB records to the chemical domain for DCAP, an initial filtering is performed to remove drugs, pesticides, and food additives that are not on the TSCA inventory. The ToxValDB records are filtered as follows:

- A combined set of drugs is created by taking the union of the FDA approved drug products,[20] the Drug Enforcement Agency (DEA) Schedule 1 through 5 lists,[21] and those listed in DrugBank.[22]
- A combined set of pesticides is created by taking the union of the Compendium of Pesticide Names[23] and the EPA Pesticide Chemical Search Database.[24]
- A list of food additives is obtained using the FDA substances added to food inventory (formerly Everything Added to Foods in the United States).[25]

The combined drug, pesticides, and food additive lists are cross-referenced with the union of chemicals listed on the TSCA non-confidential active and inactive inventories from 2021 – 2024. The ToxValDB records associated with any drug, pesticide, or food additive that was not on the TSCA active or inactive inventories are excluded from the analysis.

3.2.5. RECORD DEDUPLICATION

ToxValDB records are defined as unique records based on the original information reported by a data source, not the standardized field value it is later assigned (*e.g.,* unit conversion standardization). Only a subset of record fields available in ToxValDB are used in the DCAP process, which can lead to filtered and selected records appearing to be duplicated. To address this potential source of duplication, as ToxValDB records are selected for inclusion in DCAP, they undergo another

[20] The list of FDA approved drugs with therapeutic equivalence evaluations (i.e., FDA Orange Book) can be found at: https://comptox.epa.gov/dashboard/chemical-lists/FDAORANGE

[21] The DEA Schedule 1 through 5 drugs can be found at:
Schedule 1, https://comptox.epa.gov/dashboard/chemical-lists/DEASCHED1;
Schedule 2, https://comptox.epa.gov/dashboard/chemical-lists/DEASCHED2;
Schedule 3, https://comptox.epa.gov/dashboard/chemical-lists/DEASCHED3;
Schedule 4, https://comptox.epa.gov/dashboard/chemical-lists/DEASCHED4;
Schedule 5, https://comptox.epa.gov/dashboard/chemical-lists/DEASCHED5

[22] The list of drugs in DrugBank can be found at: https://comptox.epa.gov/dashboard/chemical-lists/DRUGBANKV2

[23] The list of pesticides in the Compendium of Pesticide Names can be found at: http://www.bcpcpesticidecompendium.org/

[24] The list of pesticides in the EPA Pesticide Chemical Search Database can be found at: https://comptox.epa.gov/dashboard/chemical-lists/EPAPCS

[25] The list of the FDA substances added to food inventory can be found at: https://comptox.epa.gov/dashboard/chemical-lists/FDAFOODSUBS

deduplication process (similar to that described in Section 3.1.1). Records within the same study group (which represents study specific fields, see Section 3.1.5) are matched to identify duplicate records that need to be further merged. Where records were merged, affected fields are maintained as a list of original values from the individual records separated by a unique delimiter to easily identify merged (*i.e.,* de-duplicated) records.

3.3. DATA STANDARDIZATION AND STUDY GROUP RECORD SELECTION

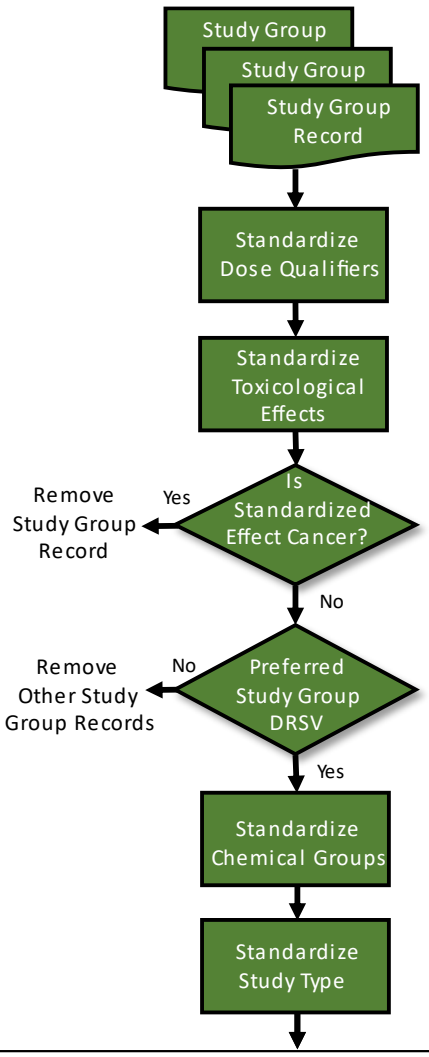
Two important steps in the DCAP process are standardizing the ToxValDB data and the selection of a preferred study group record. For standardization, the various ToxValDB sources rely on diverse data structures that are mapped to a common set of fields and use different terminology. Standardization of certain data fields is necessary for consistent interpretation and the conversion of DRSVs to $eBMD_{HED}$ values. The standardized data fields include dose qualifiers, toxicological effects, chemical group, and study type (**Fig. 3-4**). The standardized data fields do not overwrite the original ToxValDB data fields but are included in the post-standardization consolidated study group record. For selection of a preferred study group record, study groups have separate records for each DRSV. For example, a study group can have separate records for a NOAEL and LOAEL value. The selection of a single preferred study group record is necessary to allow each study group to contribute equally to the $eBMD_{HED}$ distribution for each chemical.

3.3.1. DOSE QUALIFIER STANDARDIZATION

A subset of ToxValDB records include a numeric qualifier along with the DRSV. The qualifiers include "=," "~," ">," "≥," "<," or "≤." A total of 80% of the ToxValDB records had either no qualifier or a qualifier of "=" indicating the DRSV was accurate as provided. Consistent with Aurisano et al. (Aurisano et al. 2023), the qualifier is disregarded in the DCAP analysis except in the event where the "<" qualifier accompanied a NOAEL. In such cases, the effects were assumed to occur at the lowest dose tested and the DRSV is converted to a LOAEL. The combination of a "<" and NOAEL constituted less than 2% of the records. The choice to disregard the ">" and "≥" qualifiers would result in an assumption that effects occurred at a lower dose than what was observed. For example, if the qualifier indicates that a LOAEL is > 1000 mg/kg/day, the LOAEL is assumed to be 1000 mg/kg/day, providing a protective estimate of the LOAEL from the study group. The ">" and "≥" qualifiers were present in 8% and 6% of the records, respectively.

3.3.2. TOXICOLOGICAL EFFECT STANDARDIZATION

The description of the observation that drove identification of the effect-dose linkage in each record varies across the selected data sources. For each record, the reported toxicological effect is standardized to one of the following effect categories: body weight, cancer-related, clinical chemistry, clinical signs, developmental, enzyme activity, food and/or water consumption, gross pathology, hematology, mortality/survival, multiple (*e.g.,* two or more non-cancer endpoints across different health effect categories identified at the same dose level), neurobehavior, neurotransmitter, none



Consolidated Study Group Record				
Chemical Characteristics	Study Characteristics	**Exposure Characteristics**	**Effect Characteristics**	**Source Characteristics**
DTXSID	Species, strain, sex	Exposure route	Standardized toxicological effect	Information source
CASRN	Standardized study type	Exposure method	Life stage	Year
Chemical name	Study duration class	Exposure form	Generation	
Standardized chemical group			Preferred dose response summary value	

Figure 3-4. Detailed flowchart of the standardization and study group record selection process for DCAP. The study group records from ToxValDB are standardized for dose qualifiers, toxicological effects, chemical group, and study type. A single preferred study group record and associated DRSV is selected. The combination of data fields following standardization and preferred study group record selection is referred to as a consolidated study group record.

(*i.e.,* typically associated with the NOAEL or NEL), nonneoplastic histopathology, organ weight, other, reproductive, and urinalysis. With the exception of the cancer-related effect category, the standardized toxicological effect categories are consistent with those used in Aurisano et al., Chiu et al., and the WHO/IPCS guidance document (Aurisano et al. 2023; Chiu and Slob 2015; WHO 2018).

The standardization of the toxicological effects is performed by a team of EPA toxicologists. The original toxicological effect descriptions are randomly allocated to two independent reviewers. Each reviewer assigns the reported toxicological effects into one of the standardized categories. A rubric for assigning the toxicological effects is provided in the Appendix (Section 8.2). For those standardized toxicological effects that disagree between the two reviewers, an adjudicator team member is assigned to resolve the conflict. Following the final assignment of the standardized toxicological effects, records with a cancer-related standardized effect are removed from the analysis because DCAP is not intended for cancer-related human health assessment. As indicated, standardized toxicological effects for records with NOAELs, NOELs, and NELs are automatically assigned to "none". The assignment of "none" to NOAELs, NOELs, and NELs allows greater consistency in the application of the conceptual model to convert the DRSVs to $eBMD_{HED}$ values. The assignment of "none" does not mean that toxicological effects did not occur at higher doses. For records with LOAELs, LOELs, LELs, and BMDLs where the toxicological effects are blank or not provided are assigned to "other". Records that included more than one distinct toxicological effect category at the same DRSV are assigned to "multiple". The final standardized toxicological effect calls are manually reviewed for quality and consistency.

3.3.3. HIERARCHICAL SELECTION OF A PREFERRED STUDY GROUP DRSV

The sources and records in ToxValDB often include multiple DRSVs associated with a single study group. For example, some sources may report both a NOAEL and LOAEL for a single sex in a subchronic repeat dose study. A hierarchy is used to select the single preferred DRSV for a study group. With the exception of the addition of the NEL and LEL, the hierarchy is based on common human health assessment practices (EPA 2002, 2012). The hierarchy is as follows:

1. BMDL (lowest) as the selected DRSV and, if not available, select the
2. NOAEL (highest NOAEL value below the lowest LOAEL value) as the DRSV and, if not available, select the
3. LOAEL (lowest) as the DRSV and, if not available, select the
4. NEL (highest NEL below the lowest LEL) as the DRSV and, if not available, select the
5. LEL (lowest) as the DRSV.

In some cases, multiple DRSVs are reported in the source documents representing different dosimetric adjustments. To account for this, source-adjusted HEDs are used as the preferred DRSV, followed by source-adjusted values for continuous exposure. If a source adjusted HED value is selected, then the HED adjustment in Section 4.2 is not performed. In a small number of cases,

multiple DRSVs that correspond to the same level in the hierarchy are reported in source documents within study groups. In these cases, the lowest DRSV is selected as the preferred value.

3.3.4. CHEMICAL GROUP STANDARDIZATION

In ToxValDB, the chemical identifiers are substance specific and differentiate among specific salt forms of the tested substance. Similar to the approaches taken in quantitative structure activity modeling of toxicological responses (Mansouri et al. 2024), the ToxValDB records for tested substances that vary in a particular set of counterions (*i.e.*, Li+, Na+, K+, Rb+, Cs+, Be2+, Mg2+, Ca2+, Sr2+, Ba2+, NH4+, OH-, H+) are combined into standardized substance groups. The approach is accomplished by calculating the InChIKey for each non-counterion component (*e.g.,* perfluorooctanesulfonate, DTXSID80108992) and the InChIKey for individual components of salt substances in ToxValDB (*e.g.,* potassium perfluorooctanesulfonate, DTXSID8037706). If the InChIKeys for the individual components of a salt compound match either the InChIKey of the non-counterion parent compound or one of the counterions, then that salt compound and any other salt compounds mapping to the non-counterion parent and counterions are grouped with the DTXSID of the non-counterion parent compound in the standardized substance group field. This chemical group standardization approach is used instead of QSAR-ready structures in order to prevent the grouping of substances that differ in stereochemistry as well as grouping on salts with heavy metal or organic components.

3.3.5. STUDY TYPE STANDARDIZATION

For the purposes of DCAP, the "short-term", "subchronic", "chronic", "repeat dose other", and "clinical" study types in ToxValDB are standardized to type "repeat dose", while "developmental" and "reproductive developmental" are standardized to type "reproductive developmental." For "reproductive developmental" study type records in ToxValDB with only systemic effects (*i.e.,* not reproductive or developmental endpoints) in parental or mature offspring, the study type is standardized to "repeat dose." Similarly, any records with reproductive or developmental endpoints are standardized to "reproductive developmental."

4. DERIVATION OF DATABASE-CALIBRATED TOXICITY VALUES (CTVs)

4.1. OVERVIEW

Development of the DCAP process is informed by prior established guidance, including recommendations of the WHO/IPCS as well as the methods outlined in prior publications (Aurisano et al. 2023; WHO 2018). As depicted in **Figure 4-1**, the DCAP process involves six steps that begin with the consolidated study group record DRSVs from Section 3 and end with the CTV.

- **Step 1** of the DCAP process uses the conversion factors (CFs) from the WHO/IPCS guidance to convert the DRSVs into chronic $eBMD_{HED}$ values. The CFs adjust for differences in the type of DRSV, study duration, study type, species, and toxicological effect.
- **Step 2** estimates the parameters of the distribution of $eBMD_{HED}$ values for each chemical.
- **Step 3** uses a subset of chemicals in the ToxValDB that have non-cancer human health assessments from authoritative sources (*i.e.,* authoritative chemicals; see Section 4.4.1). The authoritative chemicals are used to identify the percentile (p_{calib}) in the distribution of $eBMD_{HED}$ values that demonstrates the best concordance with the expert-selected PODs used in the derivation of toxicity values. Prior to p_{calib} estimation, the PODs from the authoritative sources are converted into chronic $eBMD_{HED,auth}$ values using the same process in Step 1.
- **Step 4** calculates the $p_{calib}{}^{th}$ percentile of $eBMD_{HED}$ distribution for each chemical, the value of which is denoted by $p_{calib}eBMD_{HED}$.
- **Step 5** determines the cPOD, defined as the lower uncertainty limit on $p_{calib}eBMD_{HED}$ for each chemical. The lower uncertainty limit incorporates the uncertainties in both the conversion (Step 1) and calibration (Step 3) steps of the process using the compounded geometric standard deviation ($GSD_{comp,j}$).[26]
- **Step 6**, the final step, the CTV is derived by applying additional UFs to the cPOD to adjust for uncertainties not yet incorporated in the DCAP process.

[26] Note that unlike the arithmetic standard deviation, the GSD is a multiplicative factor and is dimensionless.

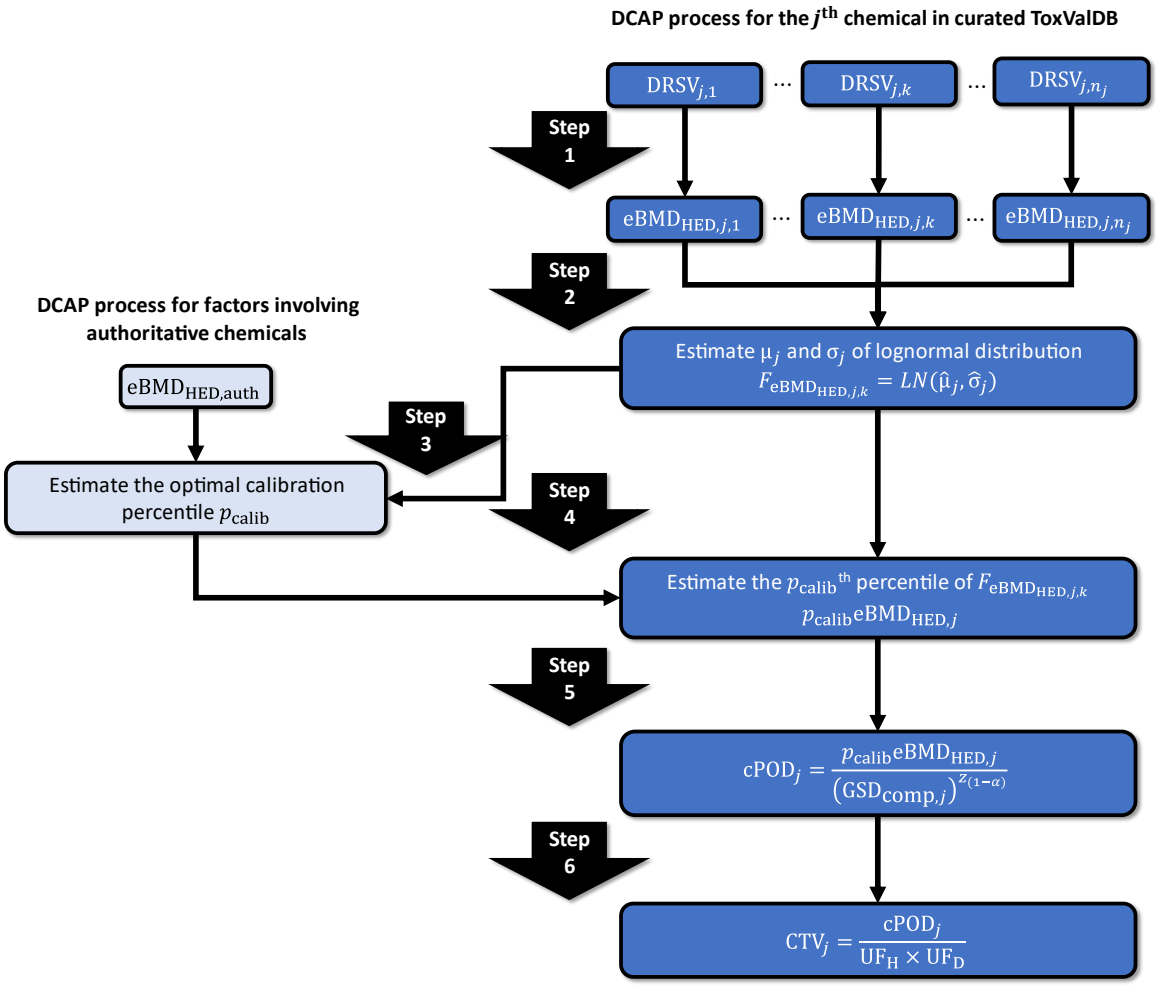


Figure 4-1. Detailed flowchart of the DCAP process to derive CTVs. The process consists of six steps. The dark blue boxes are the steps performed on all the chemicals for which DCAP assessments will be performed. The light blue boxes are the calibration step performed using the authoritative chemicals.

4.2. STEP 1: CONVERSION OF STUDY-GROUP SPECIFIC DRSV TO CHRONIC, HUMAN EQUIVALENT DOSES

The first step in the DCAP process is to apply CFs to each DRSV, based on study attributes, to derive an estimate of the $eBMD_{HED}$ under chronic exposure conditions. For each DRSV, a series of five CFs are employed (**Table 4-1**). Letting $DRSV_{j,k}$ denote the DRSV value for the k^{th} consolidated study group for the j^{th} chemical, n_j denotes the number of consolidated study groups for chemical j, and CF_l $(l = 1, \cdots, 5)$ represent the five specific conversion factor categories, the corresponding $eBMD_{HED}$ is calculated as

$$eBMD_{HED,j,k} = \frac{DRSV_{j,k}}{\prod_{l=1}^{5} CF_{j,k,l}} \left(j = 1, \cdots, J;\ k = 1, \cdots, n_j\right). \quad (1)$$

Conversion factors are obtained from the WHO IPCS guidance document and are based on distributions of historical data (IPCS, 2018). The first conversion factor (CF_1) standardizes the study

duration to its chronic equivalent. If the study duration is subchronic or clinical, CF_1 is set equal to 2. If the study duration is short-term, CF_1 is assigned a value of 5. Standardized reproductive developmental study types are not duration adjusted if the DRSV is based on an effect in offspring (Chiu et al. 2018). The second conversion factor (CF_2) adjusts for body size differences between animals and humans. Using allometric scaling, CF_2 is calculated based on the ratio of human to animal bodyweights to the 0.3 power as

$$CF_2 = \left(\frac{BW_{Human}}{BW_{Animal}}\right)^{0.3} . \quad (2)$$

For DCAP, body weight is assumed to be 80 kg for humans (EPA 2011a), 0.025 kg for mice, 0.25 kg for rats, 2 kg for rabbits, and 15 kg for dogs when calculating CF_2 (IPCS, 2018).

Table 4-1. Conversion factors used to calculate $eBMD_{HED}$ based on DRSVs[a]

l	Category	Conversion	Conversion Factor (CF)
1	Exposure duration	Chronic → Chronic	1
		Reproductive/Developmental → Chronic	1
		Subchronic/Clinical → Chronic	2
		Short-term → Chronic	5
2	Allometric scaling	Human → Human	1
		Mouse → Human	11.3
		Rat → Human	5.6
		Rabbit → Human	3.0
		Dog → Human	1.7
3	Effect level	NOAEL → NOAEL	1
		LOAEL → NOAEL	3
4A	Conceptual model (NOAEL → BMD)	Continuous (non-rep/dev)	1/3
		Continuous (rep/dev)	1/3
		Quantal-Deterministic	2/9
		Quantal-Stochastic	2/3
4B	Conceptual model (BMDL → BMD)	Continuous (non-rep/dev)	1/3
		Continuous (rep/dev)	1/3
		Quantal-Deterministic	1/9
		Quantal-Stochastic	1/3
4C[b]	Conceptual model (BMD → BMD)	No conversion required	1
5	Toxicokinetic (TK)/Toxicodynamic (TD) differences	Human → Human	1
		Non-Human → Human	1

[a] Values described in Table 4-1 are recommended values published in WHO/IPCS Guidance Document (IPCS, 2018).
[b] The conversion factor was left in the table for the sake of completeness, but the conversion factor is set to 1 since there is no conversion required.

The third conversion factor, CF_3, converts DRSVs that are LOAELs to NOAELs by dividing the LOAEL by 3 (WHO 2018). The fourth conversion factor, CF_4, translates DRSVs that are NOAELs or BMDLs to BMDs using a conceptual mathematical model based on standardized study type and

toxicological effect (Aurisano et al. 2023; WHO 2018). The conceptual mathematical models are assigned to each record based on the standardized study type and standardized toxicological effect outlined in the Appendix (Section 8.3). The fifth conversion factor, CF_5, adjusts for residual toxicokinetic/toxicodynamic differences between test animals and humans after allometric scaling. The default value of CF_5 is set equal to 1. The values in **Table 4-1** should not be directly compared with the default EPA UF values as the EPA UF values typically incorporate both the conversion and associated uncertainty. The uncertainty in the conversion factors in **Table 4-1** are incorporated in Step 5 (Section 4.6).

4.3. STEP 2: ESTIMATION OF DISTRIBUTION FOR CHEMICAL-SPECIFIC $eBMD_{HED}$ VALUES

Each chemical eligible for DCAP has a varying number of $eBMD_{HED}$ values derived from studies that may differ with respect to experimental animals, study durations, toxicological effects, and dosing regimen, as well as random variation associated with replicate experiments using the same study design. A lognormal distribution is fit to the $eBMD_{HED}$ values consistent with the choice of Aurisano et al. (Aurisano et al. 2023). The choice of a lognormal distribution is supported by previous studies that have shown the distributions of NOAEL, BMDs, and BMDL values to be consistent with lognormality (Bokkers and Slob 2005, 2007). A visual examination of normal quantile-quantile plots for individual chemicals with a sufficient number of $eBMD_{HED}$ values also does not provide strong evidence against the lognormal assumption, particularly in the central part of the distribution (see Appendix, Section 8.4).

Under the lognormal distribution, the mean ($\hat{\mu}_j$) and the standard deviation ($\hat{\sigma}_j$) for the j^{th} chemical are estimated by

$$\hat{\mu}_j = \frac{\sum_{k=1}^{n_j} \log_{10}\left(\text{eBMD}_{\text{HED},j,k}\right)}{n_j}\,, \tag{3}$$

and

$$\hat{\sigma}_j = \sqrt{\frac{\sum_{k=1}^{n_j}\left[\log_{10}\left(\text{eBMD}_{\text{HED},j,k}\right) - \hat{\mu}_j\right]^2}{n_j - 1}}\,, \tag{4}$$

respectively. The x^{th} percentile of the lognormal distribution for the j^{th} chemical is then estimated by

$$p_x\text{eBMD}_{\text{HED},j} = 10^{\hat{\mu}_j + z_x\hat{\sigma}_j}\,, \tag{5}$$

where z_x represents the z-score of the x^{th} percentile of the standard normal distribution $N(0,1)$.

While the minimum number of $eBMD_{HED}$ values required for the estimation of the parameters for the lognormal distribution is two, the DCAP process is only applied to chemicals with a minimum of five consolidated study groups. The cut-off of five consolidated study groups is implemented for three primary reasons. First, a larger number of consolidated study groups increases the stability and reliability of the DCAP process. Second, quantitative analyses demonstrate

that the downstream uncertainty calculated in Step 5 declines exponentially as the number of consolidated study groups increases and begins to level off at around five consolidated study groups. A lower cut-off would lead to potentially large uncertainty in the estimation of the DCAP parameters that define the CTV. A more detailed breakdown of the uncertainty as a function of the number of consolidated study groups is provided in the Appendix (Section 8.5). Third, a minimum of five consolidated study groups reduces the likelihood that the derivation of a CTV is from a single study. For example, a reproductive study with both male and female animals in the F_0 (parental), and F_1 (offspring) generations may be considered to have four consolidated study groups due to how they are defined in ToxValDB, even though all four DRSVs are from a single reproductive study.

4.4. STEP 3: CALIBRATION OF $eBMD_{HED}$ VALUES TO AUTHORITATIVE SOURCES

Translating the distribution of $eBMD_{HED}$ values across multiple consolidated study groups into a single value that can be used as the basis for a DCAP requires calibration to non-cancer human health assessments from authoritative sources. The chemicals with authoritative human health assessments are used to identify the percentile (p_{calib}) in the distribution of $eBMD_{HED}$ values that demonstrates the best concordance with the PODs used in the derivation of toxicity values across all authoritative chemicals.

4.4.1. AUTHORITATIVE SOURCE DESCRIPTION

For the DCAP process, the following sources from US and Canadian federal agencies are used for authoritative toxicity values:

- Agency for Toxic Substances and Disease Registry (ATSDR);
- EPA Human Health Toxicity Values (HHTVs);
- EPA Health Effects Assessment Summary Tables (HEAST);
- EPA Integrated Risk Information System (IRIS);
- EPA Provisional Peer-Reviewed Toxicity Values (PPRTVs); and
- Health Canada.

For each non-cancer human health assessment from the authoritative sources, the POD for the critical effect used in the derivation of the toxicity value is manually curated and added as a record in ToxValDB. The POD values are filtered and standardized as described in Section 3 and converted into $eBMD_{HED}$ values as described in Step 1. The corresponding ToxValDB consolidated study group record is tagged as an authoritative value for calibration. The duration corresponding to the derived toxicity value is also extracted for each associated consolidated study group record. To address cases where multiple authoritative PODs are available for a given chemical, a selection hierarchy is applied wherein PODs used in the derivation of the chronic duration toxicity value are preferentially selected over values associated with intermediate or subchronic durations. PODs used in the derivation of acute or screening-level toxicity values (*e.g.,* PPRTV appendix values) are not included as values for

calibration. When more than one value of $\text{eBMD}_{\text{HED,auth}}$ for the same duration is available for a given chemical from multiple authoritative bodies (*e.g.,* two chronic values from different authoritative sources), the average (in log scale) of these values is used.

4.4.2. SELECTION OF CALIBRATION PERCENTILE

A total of 376 chemicals were identified that have a POD used by the authoritative source as a basis for establishing an oral toxicity value. Of these, 193 chemicals have at least five consolidated study groups with DRSVs from all DCAP sources that can be used to estimate the lognormal distribution of eBMD_{HED} values. The breakdown by source of the 193 PODs includes ATSDR, 23%; EPA HHTV, 2%; EPA HEAST, 0.5%; EPA IRIS 62%, EPA PPRTV, 24%; and Health Canada, 12%.

The calibration process determines the optimal calibration percentile p_{calib} by minimizing the discordance between the values of $\log_{10}(\text{eBMD}_{\text{HED,auth}})$ calculated using DRSVs chosen by authoritative bodies and the values of $\log_{10}(p_x\text{eBMD}_{\text{HED}})$ from all DCAP sources (including authoritative sources) for these authoritative chemicals. Discordance is measured using the root mean squared difference (RMSD) between these values, given by

$$\text{RMSD} = \sqrt{\frac{\sum_{j=1}^{193}\left[\log_{10}\left(\text{eBMD}_{\text{HED,auth},j}\right) - \log_{10}\left(p_x\text{eBMD}_{\text{HED},j}\right)\right]^2}{193}}. \quad (6)$$

The RMSD provides a convenient quantitative measure of how close $p_x\text{eBMD}_{\text{HED}}$ predictions match their corresponding POD value determined by authoritative bodies.

A plot of the RMSD as a function of the calibration percentile (p_x) is shown in **Figure 4-2.** The RMSD is minimized at the 18th percentile of the eBMD_{HED} distribution. A scatterplot of $p_{18}\text{eBMD}_{\text{HED}}$ and $\text{eBMD}_{\text{HED,auth}}$ values is presented in **Figure 4-3**.

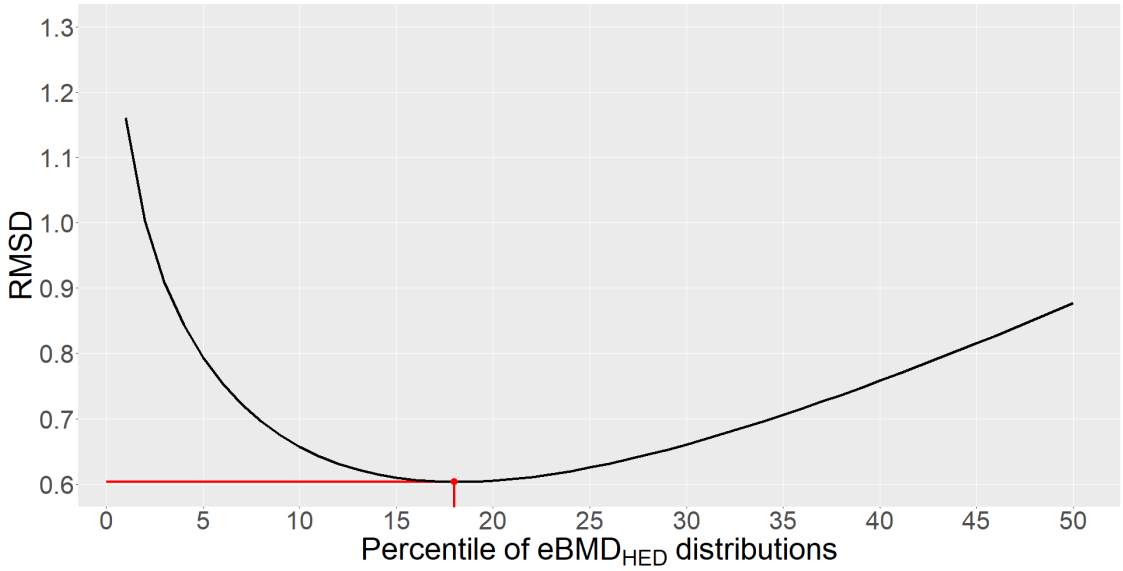


Figure 4-2. RMSD values evaluated at a range of percentiles of eBMD_{HED} distributions across 193 chemicals with toxicity values from authoritative sources. The percentile at the lowest RMSD (p_{calib} = 18) is delineated with a red line.

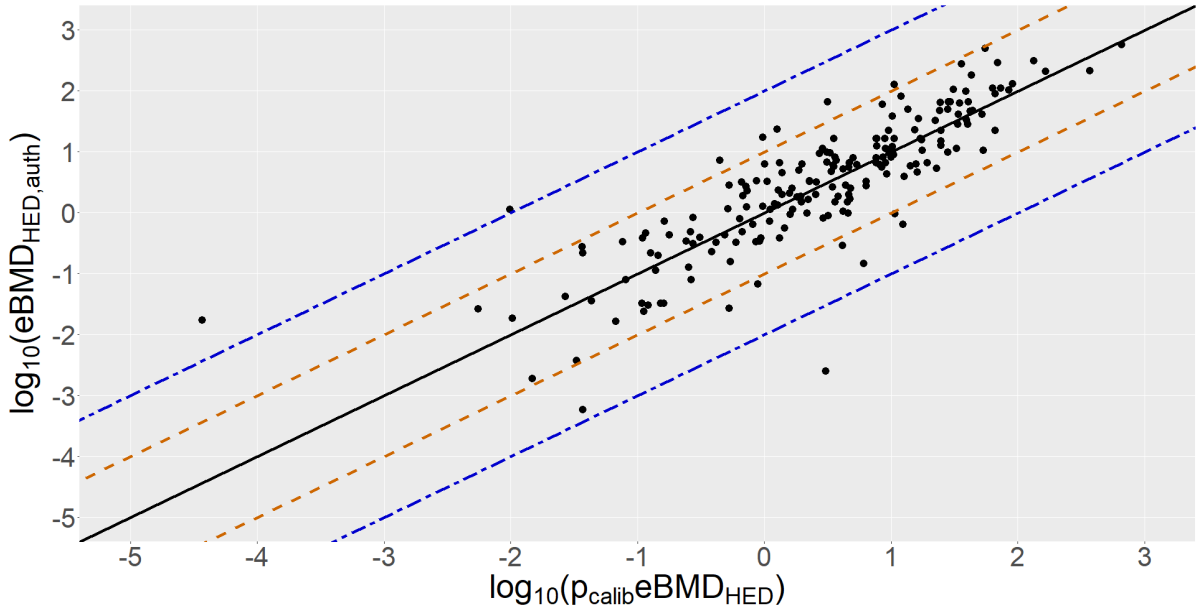


Figure 4-3. Scatterplot of $p_{\text{calib}}\text{eBMD}_{\text{HED}}$ and $\text{eBMD}_{\text{HED,auth}}$ values across 193 chemicals with toxicity values from authoritative sources.

4.5. STEP 4: CALCULATION OF CALIBRATED eBMD$_{\text{HED}}$ VALUE

The optimal calibration percentile, as derived in Step 3, is the 18$^{\text{th}}$ percentile of the eBMD_{HED} distribution for each chemical that meets the inclusion criteria for the DCAP process. The database-calibrated eBMD_{HED} value ($p_{\text{calib}}\text{eBMD}_{\text{HED}}$) for the j^{th} chemical evaluated is defined as the 18$^{\text{th}}$ percentile of the assumed lognormal distribution with estimated parameters $\hat{\mu}_j$ and $\hat{\sigma}_j$ (Eqs. 3 and 4). The $p_{\text{calib}}\text{eBMD}_{\text{HED}}$, in turn, is subsequently used to calculate the cPOD and the CTV for each chemical, as described in Sections 4.6 and 4.7, respectively.

4.6. STEP 5: CHARACTERIZATION OF UNCERTAINTY AND CALCULATION OF cPOD

The $p_{\text{calib}}\text{eBMD}_{\text{HED}}$ value for each chemical derived following Steps 1 to 4 represents an estimate of what the calibrated eBMD_{HED} value would be based on the data available in ToxValDB. However, there are two main sources of uncertainty in the $p_{\text{calib}}\text{eBMD}_{\text{HED}}$ values:

- Uncertainty in the estimation of the value of $p_{\text{calib}}\text{eBMD}_{\text{HED}}$ for the individual chemicals given their assumed distribution (propagated from the uncertainties in the estimated mean $\hat{\mu}_j$ and standard deviation $\hat{\sigma}_j$); and
- Uncertainty in determining the optimal calibration percentile p_{calib}.

The two uncertainties are discussed in more detail in Sections 4.6.1 and 4.6.2, respectively. The derivation of the combined uncertainty is described in Section 4.6.3.

4.6.1. DESCRIPTION OF THE TRADITIONAL UNCERTAINTIES INCORPORATED INTO THE CALCULATION OF THE cPOD

In traditional human health assessment, the EPA considers five main areas of uncertainty in deriving toxicity values from PODs estimated using experimental data (EPA 1994, 2002). Weight-of-evidence-based decisions inform quantitative application of UFs and are intended to account for: 1) unknown or imprecise measures of variability in sensitivity among members of the exposed human population (*i.e.,* interhuman or intraspecies variability, UF_H); 2) the uncertainty in extrapolating animal data to humans (*i.e.,* interspecies variability, UF_A); 3) the uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure to chronic/lifetime exposure (*e.g.,* extrapolating from subchronic to chronic exposure, UF_S); 4) the uncertainty in extrapolating from a LOAEL rather than from a NOAEL (UF_L), if applicable; and 5) the uncertainty associated with deficiencies or knowledge gaps in the chemical-specific database (UF_D).

The overall propagation of uncertainties considered in the calculation of the cPOD is depicted in **Figure 4-4.** Note that three of the five traditional sources of uncertainty considered in human-health assessment are incorporated directly into the calculation of the cPOD, including those traditionally covered by UF_S (*i.e.,* uncertainty in extrapolating from shorter-duration studies to chronic duration), UF_L (*i.e.,* uncertainty in extrapolating from a LOAEL to a NOAEL), and UF_A (*i.e.,* uncertainty in extrapolating from an experimental animal to a human). Additional sources of uncertainty (*e.g.,* uncertainty in the calibration process, denoted by GSD_{disc})[27] are also incorporated into the cPOD. The remaining two traditional sources of uncertainty, UF_H (*i.e.,* uncertainty in human variability) and UF_D (*i.e.,* uncertainty in the toxicological database), are incorporated at Step 6.

4.6.1.1. SUBCHRONIC-TO-CHRONIC DURATION UNCERTAINTY (UF_S)

EPA defines a chronic duration as repeated exposure by the oral, dermal, or inhalation route for more than approximately 10% of the life span in humans, corresponding to more than approximately 90 days to 2 years in typically used laboratory animal species (EPA 2002, 2011a, b). Subchronic duration is defined as repeated exposure by the oral, dermal, or inhalation route for more than 30 days, up to approximately 10% of the life span in humans, corresponding to more than 30 days up to approximately 90 days in traditional laboratory animal species (EPA 2002, 2011a). In traditional risk assessment practice, if no chronic duration study is available, information from a subchronic study may be used to support the derivation of an RfD with the application of a UF_S to the subchronic POD. In the context of the DCAP, duration adjustment to a chronic value is applied (in Step 1) to the DRSV via application of the appropriate duration-adjustment conversion factor (CF_1) and incorporation of its associated uncertainty (GSD_{CF1}) into GSD_{μ} below.

[27] The "disc" in GSD_{disc} refers to discordance.

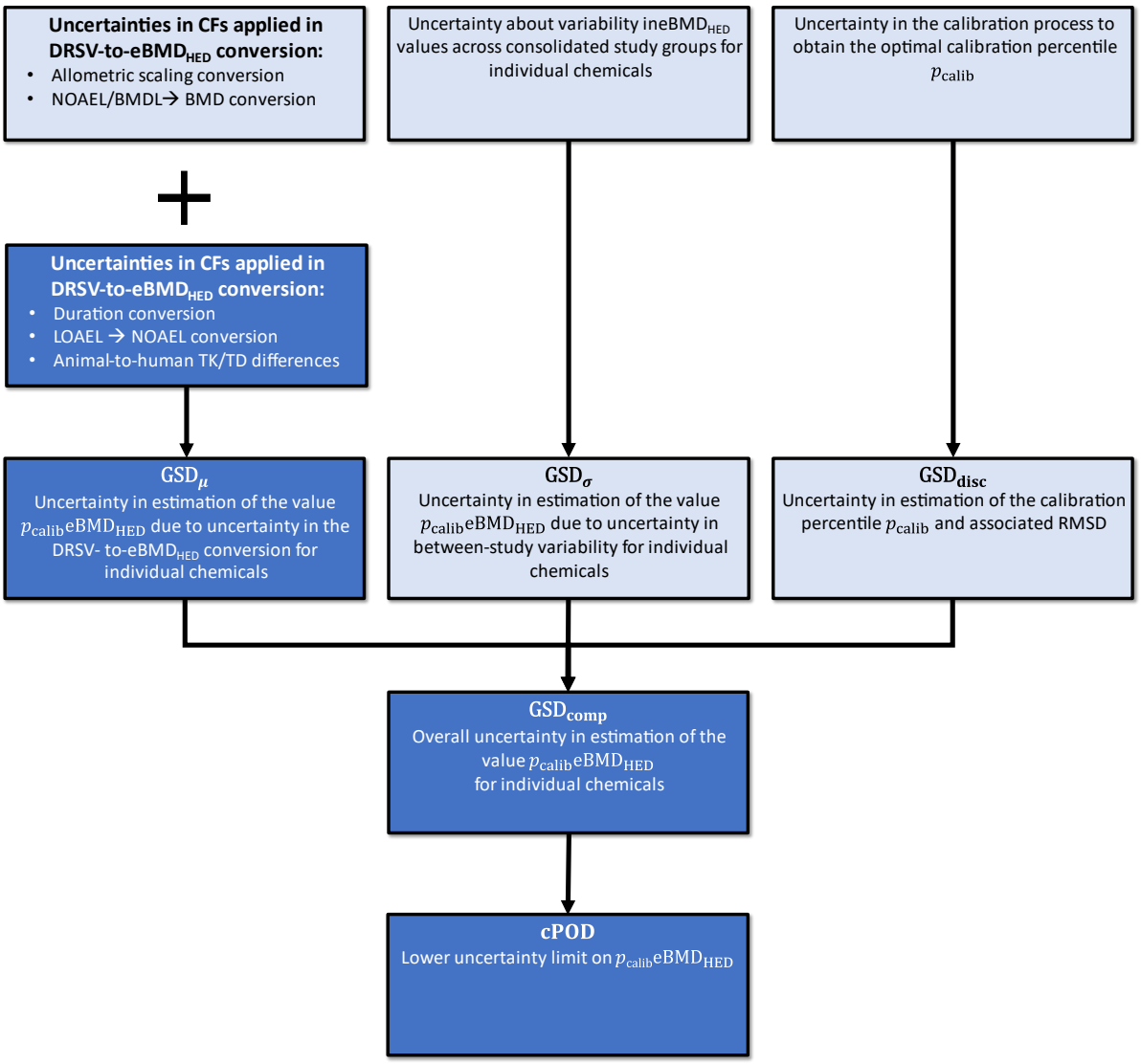


Figure 4-4. Flowchart depicting propagation of uncertainties in the development of the cPOD. The dark blue box lists 3 of the 5 uncertainties typically considered in a traditional human health assessment. The light blue boxes are additional uncertainties considered in DCAP. The arrows indicate where the different uncertainties are propagated and captured in the process of developing a cPOD.

4.6.1.2. LOAEL-TO-NOAEL UNCERTAINTY (UF_L)

The current EPA approach for dose response assessment prioritizes the application of BMD modeling to identify potential PODs (*e.g.,* BMDL) for effects. If dose-response data are not amenable to modeling, a NOAEL may be identified as a POD (*i.e.,* traditionally the highest NOAEL under the lowest LOAEL across the profile of effects for a given chemical). When a BMDL or NOAEL is not available, a LOAEL can be used, but a LOAEL-to-NOAEL uncertainty factor (UF_L) is applied to derive a non-cancer reference value. This UF_L is employed to estimate an exposure level below the LOAEL expected to be in the range of a NOAEL. Based on the effect type, study type, and assigned conceptual model (**Table 4-1**), the reported DRSV is extrapolated to a BMD equivalent for DCAP. In Step 1, DRSV

point estimates across available consolidated study groups such as LOAELs and NOAELs are utilized to identify an estimated BMD value (*i.e.,* $eBMD_{HED}$), with conversion applied via CF_4. The associated uncertainty in CF_4 is incorporated into GSD_μ below (Section 4.6.2.1).

4.6.1.3. ANIMAL-TO-HUMAN INTERSPECIES UNCERTAINTY (UF_A)

The interspecies UF_A is applied to account for the extrapolation of laboratory animal data to humans, and it is generally presumed to include cross-species TK and TD uncertainties. In implementing Step 1 of the DCAP process, allometric scaling conversion for TK is applied using CF_2. The remaining TD differences between humans and animals are accounted for, in part, during Step 1 of the DCAP process via application of CF_5. The uncertainties associated with CF_2 (TK) and CF_5 (TD) are incorporated into GSD_μ as described below (Section 4.6.2.1).

4.6.2. UNCERTAINTY IN THE ESTIMATION OF THE PERCENTILE OF DISTRIBUTION FOR CHEMICAL SPECIFIC $eBMD_{HED}$ VALUES

For each chemical, the $eBMD_{HED}$ value associated with the optimal calibration percentile, $p_{\text{calib}}eBMD_{HED,j}$, is completely specified by the mean (μ_j) and the standard deviation (σ_j) of the lognormal distribution. The uncertainty in the estimation of μ_j and σ_j propagates to uncertainty in the estimation of $p_{\text{calib}}eBMD_{HED,j}$. GSD_{μ_j} and GSD_{σ_j} denote the uncertainty in the estimation of $p_{\text{calib}}eBMD_{HED,j}$ due to uncertainties propagated from the estimation of μ_j and σ_j, respectively. The overall uncertainty in the estimation of $p_{\text{calib}}eBMD_{HED,j}$, based on the assumed distribution of $eBMD_{HED}$ values, is given by

$$GSD_{p_{\text{calib}}eBMD_{HED,j}} = 10^{\sqrt{\log_{10}\left(GSD_{\mu_j}\right)^2+\log_{10}\left(GSD_{\sigma_j}\right)^2}}. \quad (7)$$

This result holds under the assumption that $\hat{\mu}_j$ and $\hat{\sigma}_j$ are statistically independent, which is the case for the normal distribution (Hogg et al. 2019). The next sections describe the derivation of these GSDs.

4.6.2.1. DERIVATION OF $GSD_{\mu j}$

For the j^{th} chemical, GSD_{μ_j} represents the uncertainty in the estimation of $p_{\text{calib}}eBMD_{HED,j}$ due to the estimation of μ_j arising from the uncertainty surrounding the CFs applied to each DRSV. For each chemical, derivation of GSD_{μ_j} is performed in two steps: the first is to combine uncertainties surrounding the five CFs ($GSD_{CF_l}; l = 1, \cdots, 5$) into an overall uncertainty for DRSV-to-$eBMD_{HED}$ conversion ($GSD_{CF_{\text{total}}}$); the second is to quantify the uncertainty about $p_{\text{calib}}eBMD_{HED,j}$ due to $GSD_{CF_{\text{total}}}$ using a bootstrapping method.

As outlined in Step 1, the five CFs are designed to standardize various study designs to chronic human equivalent doses. The uncertainties associated with the five CFs are provided in **Table 4-2**. Uncertainty about the CFs is gauged by examining historical variation in the parameters used to determine the CFs across chemicals. The previously described uncertainty distributions for the CFs are assumed to follow a lognormal distribution and the values defined in Chiu and Slob and the

WHO/IPCS guidance (Chiu and Slob 2015; WHO 2018). For example, in gauging uncertainty about CF_1, the WHO used a value of 4 to represent the ratio of the 95th to 50th percentiles (P_{95}/P_{50}) in the distribution of subchronic-to-chronic differences across chemicals from historical studies. This corresponds to a lognormal distribution with a geometric mean (GM) of 1 and a geometric standard deviation (GSD) of 2.32 (*i.e.,* $(P_{95}/P_{50})^{1/z_{0.95}} = 4^{1/1.645}$). GSD_{CF_1} reflects the uncertainty in converting subchronic or short-term study results to their chronic equivalents; GSD_{CF_2} accounts for the (non-chemical specific) uncertainty in sensitivity between test animals and humans due to physiological differences; GSD_{CF_3} incorporates the uncertainty in converting the LOAEL-based DRSVs to an equivalent NOAEL; $GSD_{CF_{4A}}$ and $GSD_{CF_{4B}}$ quantify the uncertainty surrounding the conversion from NOAEL-to-BMD and BMDL-to-BMD, respectively, for the various critical endpoints and measured responses; and GSD_{CF_5} represents the residual uncertainty arising from any remaining toxicokinetic and toxicodynamic differences between test animals and humans, beyond the uncertainties associated with allometric scaling.

Table 4-2. Uncertainties associated with the conversion factors used to calculate $eBMD_{HED}$ based on DRSVs[a]

l	Category	Conversion	Uncertainty in CF (P_{95}/P_{50})	GSD_{CF_l} $\left(\frac{P_{95}}{P_{50}}\right)^{1/z_{0.95}}$
1	Exposure duration	Chronic → Chronic	NA	NA
		Reproductive/Developmental → Chronic	NA	NA
		Subchronic/Clinical → Chronic	4	2.32
		Short-term → Chronic	8	3.54
2	Allometric scaling	Human → Human	NA	NA
		Mouse → Human	1.4	1.22
		Rat → Human	1.3	1.15
		Rabbit → Human	1.2	1.09
		Dog → Human	1.1	1.04
3	Effect level	NOAEL → NOAEL	NA	NA
		LOAEL → NOAEL	3	1.95
4A	Conceptual model (NOAEL → BMD)	Continuous (non-rep/dev)	4.7	2.56
		Continuous (rep/dev)	7.0	3.26
		Quantal-Deterministic	5.0	2.66
		Quantal-Stochastic	4.7	2.56
4B	Conceptual model (BMDL → BMD)	Continuous (non-rep/dev)	3	1.95
		Continuous (rep/dev)	3	1.95
		Quantal-Deterministic	1.5	1.28
		Quantal-Stochastic	3	1.95
4C	Conceptual model (BMD → BMD)	No conversion required	NA	NA
5	TK/TD differences	Human → Human	NA	NA
		Non-Human → Human	3	1.95

[a] Values in Table 4-2 are recommended values published in WHO/IPCS Guidance Document (IPCS, 2018). GSD_{CF_l}: geometric standard deviation about l^{th} conversion factor.

For the k^{th} study group, the total uncertainty due to the combination of the five CFs can be expressed as

$$\log_{10}\left(\text{GSD}_{\text{CF}_{\text{total}},j,k}\right) = \sqrt{\sum_{l=1}^{5}\left[\log_{10}\left(\text{GSD}_{\text{CF}_l,j,k}\right)\right]^2} \,. \tag{8}$$

A bootstrap approach with $n_B = 10{,}000$ iterations is employed to obtain an uncertainty distribution of the sample mean $\hat{\mu}_j$. For each bootstrap sample $b = 1, \cdots, n_B$, the following bootstrap algorithm is applied.

1. For each chemical, obtain a random sample of size n_j from the distribution

$$r_{j,k,b} \sim N\left(\log_{10}\left(\text{eBMD}_{\text{HED},j,k}\right), \log_{10}\left(\text{GSD}_{\text{CF}_{\text{total}},j,k}\right)\right). \tag{9}$$

2. Calculate the bootstrapped sample mean $\hat{\mu}_{j,b}$ as

$$\hat{\mu}_{j,b} = \frac{\sum_{k=1}^{n_j} r_{j,k,b}}{n_j} \,. \tag{10}$$

3. Derive the b^{th} bootstrap percentile of $\text{eBMD}_{\text{HED},j}$ as

$$p_{18}\text{eBMD}_{\text{HED},j,b} = q_{18}\, LN\left(\hat{\mu}_{j,b}, \hat{\sigma}_j\right). \tag{11}$$

Let $\hat{P}_{2.5,\mu_j}$ and $\hat{P}_{97.5,\mu_j}$ be the 2.5th and 97.5th percentiles of the bootstrap distribution of sample means for chemical *j*, corresponding to the 250th smallest and 9,750th largest $\hat{\mu}_{j,b}$, respectively. Using these two bounds on the uncertainty in estimating $p_{\text{calib}}\text{eBMD}_{\text{HED}}$ for the j^{th} chemical, resulting from the uncertainty associated with the estimation of the central tendency (mean) across study groups, denoted by GSD_{μ_j}, is calculated as

$$\text{GSD}_{\mu_j} = \left(\frac{\hat{P}_{97.5,\mu_j}}{\hat{P}_{50\mu_j}}\right)^{\frac{1}{z_{0.975}}} \times \left(\frac{\hat{P}_{50,\mu_j}}{\hat{P}_{2.5\mu_j}}\right)^{\frac{1}{z_{0.975}}} = \left(\frac{\hat{P}_{97.5,\mu_j}}{\hat{P}_{2.5\mu_j}}\right)^{\frac{1}{2\times z_{0.975}}} \,. \tag{12}$$

[As noted above, the two intermediate ratios in Eq. 12 effectively provide the upper and lower bounds needed to characterize the uncertainty in $p_{\text{calib}}\text{eBMD}_{\text{HED}}$.] For study groups in which two conceptual models have been assigned, Step 1 above is modified to use 50% of the bootstrap samples derived under conceptual model 1, with the remaining 50% based on conceptual model 2.

4.6.2.1. DERIVATION OF $\text{GSD}_{\sigma j}$

Under the assumption of lognormality for eBMD_{HED} values, the statistic S_j^2, among the n_j values for the j^{th} chemical, follows a (scaled) chi-square distribution with

$$\frac{(n_j-1)S_j^2}{\sigma_j^2} \sim \chi^2_{n_j-1}\,. \tag{13}$$

Two-sided 95% confidence limits for σ_j are then defined as

$$\left(\hat{\sigma}_{j,2.5\%}, \hat{\sigma}_{j,97.5\%}\right) = \left(\sqrt{\frac{(n_j-1)\hat{\sigma}_j^2}{\chi^2_{97.5\%,(n_j-1)}}}, \sqrt{\frac{(n_j-1)\hat{\sigma}_j^2}{\chi^2_{2.5\%,(n_j-1)}}}\right), \tag{14}$$

where $\chi^2_{2.5\%,(n_j-1)}$ and $\chi^2_{97.5\%,(n_j-1)}$ represent the 2.5th and 97.5th percentiles of the chi-square distribution with $n_j - 1$ degrees of freedom, respectively. The lower 2.5th confidence limit on the value of $p_{\text{calib}}\text{eBMD}_{\text{HED},j}$ incorporating uncertainty in the estimation of σ_j, denoted by $\hat{P}_{2.5,\sigma_j}$, is defined as the p_{calib}th percentile of a lognormal distribution with mean $\hat{\mu}_j$ and standard deviation $\hat{\sigma}_{j,97.5\%}$. Similarly, the upper 97.5th confidence limit ($\hat{P}_{97.5,\sigma_j}$) is defined as the p_{calib}th percentile of a lognormal distribution with mean $\hat{\mu}_j$ and standard deviation $\hat{\sigma}_{j,2.5\%}$. Using these two confidence limits, the uncertainty in estimating $p_{\text{calib}}\text{eBMD}_{\text{HED}}$ for the j^{th} chemical, resulting from the uncertainty associated with the estimation of the variability across study groups, denoted by GSD_{σ_j}, is calculated as

$$\text{GSD}_{\sigma_j} = \left(\frac{\hat{P}_{97.5,\sigma_j}}{\hat{P}_{2.5,\sigma_j}}\right)^{\frac{1}{2\times z_{0.975}}}. \tag{15}$$

4.6.3. UNCERTAINTY ASSOCIATED WITH DISCORDANCE BETWEEN PREDICTED AND AUTHORITATIVE eBMD_{HED} VALUES

As discussed in Section 4.4.2, differences between $p_{\text{calib}}\text{eBMD}_{\text{HED}}$ and $\text{eBMD}_{\text{HED,auth}}$, as reflected in the RMSD evaluated at the optimal calibration percentile, provide a measure of discordance between these predicted and curated authoritative values. As the optimal calibration percentile is estimated during the calibration process, it is also subject to uncertainty. This uncertainty can be evaluated using a cross-validation process in which the data are randomly divided into two halves. The impact of different splits to the data is provided in the Appendix (Section 8.6). The first set, called the training set, is used to estimate the optimal percentile, and the second set, called the test set, is used to evaluate discordance between predicted and actual $\text{eBMD}_{\text{HED,auth}}$ values. Repeating this cross-validation process 10,000 times generated an empirical distribution of p_{calib} values and associated RMSDs. The median, 5th, and 95th percentiles for the RMSD are 0.614, 0.504, and 0.701, respectively. The uncertainty associated with the RMSD, measuring the error when predicting the authoritative eBMD_{HED} values in the calibration process, is provided by the GSD_{disc} and is estimated with the 95th percentile as the upper bound of resampled RMSD values given by

$$\text{GSD}_{\text{disc}} = 10^{\text{RMSD}^{95\text{th Percentile}}} = 10^{0.701} = 5.02. \tag{16}$$

4.6.4. COMBINING UNCERTAINTIES ASSOCIATED WITH DISCORDANCE AND DISTRIBUTION OF $eBMD_{HED}$ VALUES AND CALCULATING THE cPOD

For each chemical, estimation of the $p_{\text{calib}}\text{eBMD}_{\text{HED}}$ has two major sources of uncertainty. One is the uncertainty in the ability for $p_{\text{calib}}\text{eBMD}_{\text{HED}}$ to predict chronic, BMD_{HED} values typically used in human health risk assessment. This uncertainty is quantified using GSD_{disc} (which is considered universal across all chemicals). Another source of uncertainty results from the estimation of the value of $p_{\text{calib}}\text{eBMD}_{\text{HED}}$ for individual chemicals of interest (which is chemical-specific) given the assumed distribution and available $eBMD_{HED}$ values. This uncertainty is measured by $GSD_{p_{\text{calib}}\text{eBMD}_{\text{HED},j}}$. Assuming that these two uncertainties are statistically independent, the compounded uncertainty about $p_{\text{calib}}\text{eBMD}_{\text{HED},j}$, denoted by $GSD_{\text{comp},j}$, is calculated using

$$\log_{10}\left(\text{GSD}_{\text{comp},j}\right) = \sqrt{\left[\log_{10}\left(\text{GSD}_{p_{\text{calib}}\text{eBMD}_{\text{HED},j}}\right)\right]^2 + \left[\log_{10}\left(\text{GSD}_{\text{disc}}\right)\right]^2}. \quad (17)$$

The 95th lower uncertainty limit on $p_{\text{calib}}\text{eBMD}_{\text{HED}}$, denoted by cPOD, is then obtained using

$$\text{cPOD}_j = \frac{p_{\text{calib}}\text{eBMD}_{\text{HED}}}{\left(\text{GSD}_{\text{comp},j}\right)^{z_{0.95}}} = \frac{p_{\text{calib}}\text{eBMD}_{\text{HED}}}{\left(\text{GSD}_{\text{comp},j}\right)^{1.645}}. \quad (18)$$

The cPOD is defined as the lower uncertainty limit of the value associated with the calibrated percentile of a distribution of chronic duration $eBMD_{HED}$ values derived from multiple human health relevant studies. The percentile has been calibrated to PODs for critical effects from select authoritative sources. The cPOD is not necessarily associated with a specific hazard or adverse effect, nor has a formal confidence evaluation been performed on the studies underpinning the distribution of $eBMD_{HED}$ values.

4.6.5. ADDITIONAL EXCLUSION CRITERION FOR DCAP

As discussed in Section 4.3, the DCAP process is applied to chemicals with DRSVs obtained from five or more consolidated study groups. This restriction is applied to reduce the uncertainty when deriving the CTV and reduce the likelihood of having only DRSVs derived from a single study. In addition to this qualitative restriction, it is also useful to include a quantitative restriction on the degree of uncertainty associated with DRSVs for a given chemical. **Figure 4-5** displays the boxplots of $\log_{10}\left(\text{GSD}_{p_{\text{calib}}\text{eBMD}_{\text{HED}}}\right)$ values grouped by the number of consolidated study groups used to calculate cPOD values for each chemical. As seen in this figure, the values of $GSD_{p_{\text{calib}}\text{eBMD}_{\text{HED}}}$ become smaller as the number of consolidated study groups increases; the maximum uncertainty occurred with five consolidated study groups, with a maximum $\log_{10}\left(\text{GSD}_{p_{\text{calib}}\text{eBMD}_{\text{HED}}}\right)$ of slightly greater than one. Based on the results**,** a quantitative restriction on the degree of uncertainty associated with DRSVs for a given chemical, as measured using $GSD_{p_{\text{calib}}\text{eBMD}_{\text{HED}}}$, is set at 10, corresponding to a maximum value of $\log_{10}\left(\text{GSD}_{p_{\text{calib}}\text{eBMD}_{\text{HED}}}\right)$ of one. As a result, one additional chemical is excluded

from the DCAP process. While the DCAP process is applied only to chemicals with a minimum of five DRSVs, sensitivity analyses showing the increased uncertainty that would accrue if chemicals with fewer than five consolidated study groups, each its DRSV, are considered as candidates for DCAP is presented in the Appendix (Section 8.5).

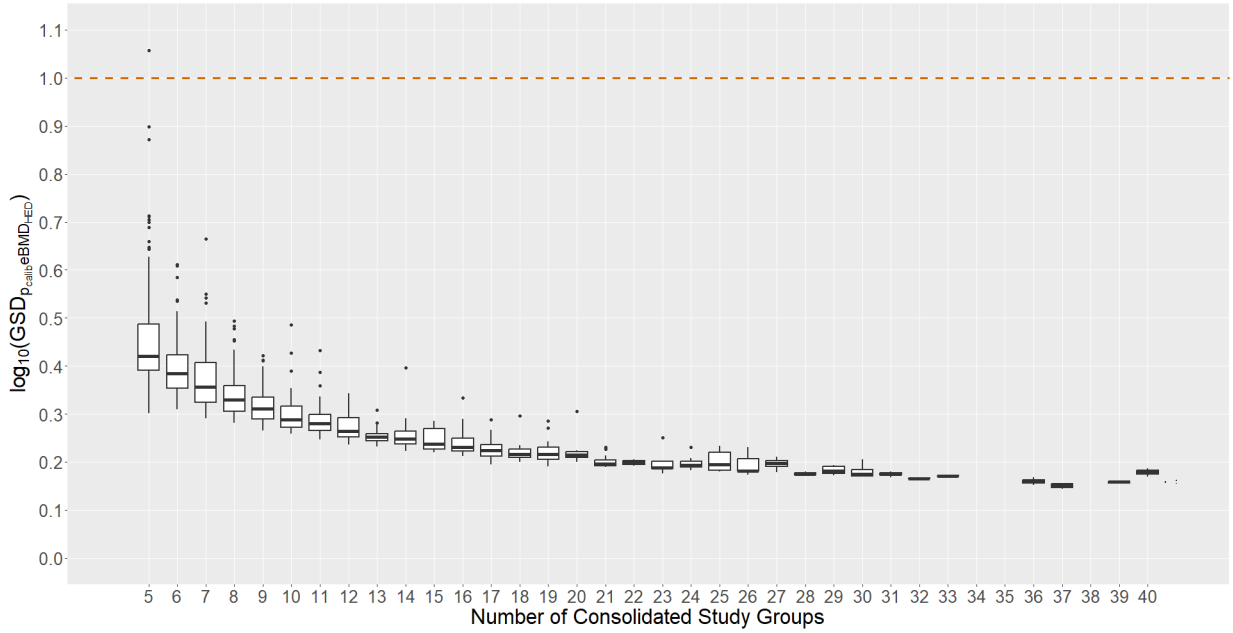


Figure 4-5. Boxplots of $\mathrm{GSD}_{p_{\mathrm{calib}}\mathrm{eBMD}_{\mathrm{HED}}}$ stratified by the number of consolidated study groups, each with a DRSV, for a given chemical. The orange dotted line represents the threshold of $\mathrm{GSD}_{p_{\mathrm{calib}}\mathrm{eBMD}_{\mathrm{HED}}} = 10$.

4.7. STEP 6: CALIBRATED TOXICITY VALUES

As described in Step 5, three of the five traditional sources of uncertainty (UF_A, UF_S, and UF_L) are addressed via a series of conversion factors and their associated uncertainties in the derivation of a cPOD. The remaining two sources of uncertainty (UF_H and UF_D) are incorporated directly in the calculation of the CTV (**Fig. 4-6**). To incorporate these sources of uncertainty, standard uncertainty factors of 10 are generally recommended in the absence of chemical-specific data or if uncertainty is not comprehensively addressed.[28]

4.7.1. INTRASPECIES VARIABILITY UNCERTAINTY FACTOR (UF_H)

The intraspecies UF_H is applied to account for variation in susceptibility within the human population (interindividual variability) and the possibility (given a lack of relevant data) that the database available is not representative of the exposure/dose response relationship in the subgroups

[28] While not utilized in the DCAP workflow, it should be noted that an uncertainty factor of 3 is used in place of half-power values (*i.e.,* $10^{0.5}$) if some aspect(s) of an uncertainty factor is addressed.

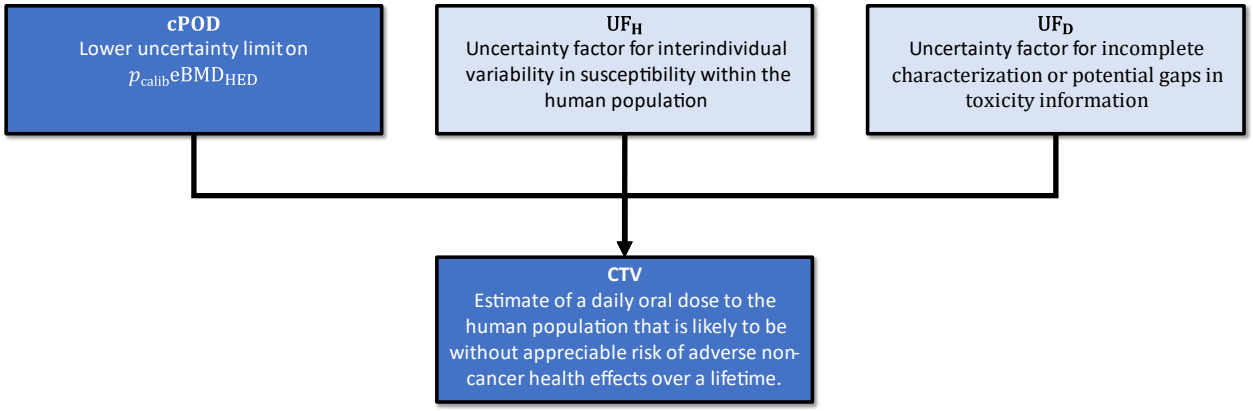


Figure 4-6. Flowchart depicting application of uncertainty factors in the development of the CTV. The light blue box lists the remaining two of the five uncertainties typically considered in a traditional human health assessment. See Fig. 4-5 for the calculation of the cPOD.

of the human population that are most sensitive to the health hazards of the chemical being assessed. As the toxicity value is defined to be applicable to "susceptible subgroups," the UF_H is used to account for uncertainty in that regard and may be presumed to entail aspects of both toxicokinetics (TK) and toxicodynamics (TD) within/across a population. In the EPA guidance (EPA 2014), the adjustment of the intraspecies UF_H from 10 should be considered only if data are sufficiently representative of the exposure/dose response relationship for the most susceptible human (sub)population(s) (*e.g.*, early and late life stages)(EPA 2000). For the DCAP approach, a UF_H of 10 is applied to all chemicals.

4.7.2. DATABASE UNCERTAINTY FACTOR (UF_D)

In traditional human health assessment, the UF_D is intended to account for the potential for deriving an under-protective RfD as a result of an incomplete characterization of the chemical's toxicity. In deciding to apply this factor to account for deficiencies in the available data set and in identifying its magnitude, the Agency recommends considering both the data lacking and the data available for health outcome domains, tissues, or organ systems, as well as life stages (EPA 2000). In addition to identifying data gaps in toxicity information, a database UF would still be applied if the data are available but considered to be low confidence (EPA 2022). In the assembly and integration of available hazard data for DCAP, no formal confidence evaluation is performed on the studies included in the dataset underpinning the distribution of $eBMD_{HED}$ values. To account for this lack of qualitative confidence characterization of the hazard data, and potential data gaps in the underlying toxicity database, a low confidence is assumed and a UF_D of 10 is applied to all chemicals. An alternative approach to the UF_D of 10 was considered and provided in the Appendix (Section 8.7).

4.7.3. DERIVATION OF CALIBRATED TOXICITY VALUE

Using the cPOD defined by Eq. (18), the value of the CTV can be derived based on the following equation:

$$\text{CTV} = \frac{\text{cPOD}}{\text{UF}_\text{A}^* \times \text{UF}_\text{S}^* \times \text{UF}_\text{L}^* \times \text{UF}_\text{H}\,(10) \times \text{UF}_\text{D}\,(10)} = \frac{\text{cPOD}}{100}\,. \tag{19}$$

The UF_A, UF_S, and UF_L are labeled with an asterisk to denote that these uncertainties are incorporated upstream in the workflow when calculating the cPOD (and each has the value of 1 for the purpose of Eq. 19). The UF_H and UF_D have default values of 10. In the context of DCAP, the CTV is defined as an estimate of a daily oral dose to the human population that is likely to be without appreciable risk of adverse non-cancer health effects over a lifetime. The CTV is derived from a cPOD with uncertainties incorporated that reflect the limitations of the data used.

4.8. EFFECTIVE COMPOSITE UNCERTAINTY ADJUSTMENT IN THE CTV

The combined uncertainty in traditional EPA human health assessments is the multiplicative product of the five UFs and is referred to as the composite UF. In DCAP, the multiplicative product of UF_H and UF_D (10 X 10 = 100) in the derivation of the CTV should not be compared with the composite uncertainties from the traditional EPA human health assessments because it is limited to only two of the five traditional sources of uncertainty. A more analogous value to the composite uncertainty in traditional EPA human health assessments is the effective composite uncertainty adjustment (ECUA), calculated as

$$\text{ECUA} = \frac{p_{\text{calib}}\text{eBMD}_{\text{HED}}}{\text{CTV}}\,. \tag{20}$$

Among the 193 chemicals with authoritative toxicity values included in the calibration step, a total of 89 have either IRIS or PPRTV RfD values. **Table 4-3** provides the summary statistics of composite UFs applied to derive the 89 IRIS and PPRTV RfD values, as well as the ECUA values in DCAP. The median ECUA value for DCAP is approximately 1.8-fold higher than the median composite UF values for IRIS and PPRTV (1,756 vs. 1,000), while the 25th percentile value is 5- to 16-fold higher for DCAP (1,636 vs. 300 or 100). The 75th percentile value for DCAP (1,815) is between that of IRIS (1,000) and PPRTV (3,000).

Table 4-3. Summary statistics of the composite UFs and corresponding EUCA values for IRIS and PPRTV chemicals used in the calibration process.

Data source	n	Min.	25%	Median	75%	Max.
IRIS ($UF_{composite}$)	56	3	100	1,000	1,000	10,000
PPRTV ($UF_{composite}$)	33	30	300	1,000	3,000	3,000
DCAP (ECUA)	89	1,467	1,636	1,756	1,815	2,844

The ECUA is partitioned into three components: GSD_{comp}, UF_H, and UF_D, and calculated as

$$\text{ECUA} = \text{GSD}_{\text{comp}}^{z_{0.95}} \times \text{UF}_\text{H} \times \text{UF}_\text{D}\,. \tag{21}$$

The relative contribution of $\mathrm{GSD}_{\mathrm{comp}}$, UF_{H}, and UF_{D} to the overall uncertainty adjustment can be described using their respective log-reductions. For example, $\mathrm{UF}_{\mathrm{H}} = 10$ and $\mathrm{UF}_{\mathrm{D}} = 10$ indicate that they each reduce the CTV by $\log_{10}(10) = 1$ order of magnitude (OM), and therefore their relative contribution can be calculated as

$$\frac{\log_{10}(\cdot)}{\log_{10}\left(\mathrm{GSD}_{\mathrm{comp}}^{z_{0.95}} \times \mathrm{UF}_{\mathrm{H}} \times \mathrm{UF}_{\mathrm{D}}\right)}, \tag{22}$$

where $\log_{10}(\cdot)$ is either $\log_{10}(\mathrm{GSD}_{\mathrm{comp}}^{z_{0.95}})$, $\log_{10}(\mathrm{UF}_{\mathrm{H}})$, or $\log_{10}(\mathrm{UF}_{\mathrm{D}})$. Similarly, the relative contribution from all uncertainty components that constitute $\mathrm{GSD}_{\mathrm{comp}}$ can be obtained by setting the respective GSD values to be one (*i.e.,* $\log_{10}(1) = 0$) and comparing the composite uncertainty adjustment values with and without these factors.

Figure 4-7 shows the relative percent contribution to the ECUA for each of these components across 193 chemicals used in the calibration process. The uncertainties around the CFs, denoted by $\mathrm{GSD}_{\mathrm{CF}_1}, \cdots, \mathrm{GSD}_{\mathrm{CF}_5}$, have relatively small contributions individually (their median values are less than 1%); however, their combined contribution, represented by the GSD_{μ}, ranges from 0.2% to 5.0%. Between GSD_{μ} and GSD_{σ}, the two components that constitute the $\mathrm{GSD}_{p_{\mathrm{calib}}\mathrm{eBMD}_{\mathrm{HED}}}$, GSD_{μ} is greater than GSD_{σ} in the majority of the cases, though there are several chemicals in which GSD_{σ} is the dominant factor in determining the value of $\mathrm{GSD}_{p_{\mathrm{calib}}\mathrm{eBMD}_{\mathrm{HED}}}$. $\mathrm{GSD}_{\mathrm{disc}}$ is greater than the $\mathrm{GSD}_{p_{\mathrm{calib}}\mathrm{eBMD}_{\mathrm{HED}}}$ in the majority of the cases with a median value of 22% and 3.8%, respectively. $\mathrm{GSD}_{\mathrm{comp}}$, the combined GSD of $p_{\mathrm{calib}}\mathrm{eBMD}_{\mathrm{HED}}$ and calibration, contributes 37% to 51% of the overall uncertainty in the DCAP process.

It is also possible to obtain a combined contribution of various sources of uncertainty that reflect different breakdowns of the uncertainty. On the far-right side of **Figure 4-7**, the uncertainties considered in the DCAP process are partitioned into two categories: five uncertainties considered in the traditional human health assessment (UF_{A}, UF_{L}, UF_{S}, UF_{H}, and UF_{D}), denoted as "Combined Traditional Sources"; and those that constitute additional sources of uncertainty specific to the DCAP process, denoted as "Combined DCAP-Specific Sources." Considering the relative contributions of the uncertainties in DCAP shows that when considering only the five sources of uncertainty considered in the traditional human health assessment, these uncertainties contribute approximately 50 – 63% of the adjustment expressed on the log-scale. The remaining adjustment on the log-scale is from other sources of uncertainty associated with the DCAP process. Note that the ECUA calculation contains a series of non-linear operations (*e.g.,* sum of squares, bootstrap, and percentile calculation), which are not simply multiplicative combinations of uncertainty contributing factors. This means that the results are not simply additive combinations when measured on the log-scale. As a result, relative contributions to the log-scaled value of ECUA do not add up to 100% as would be expected for purely multiplicative combinations of adjustment factors.

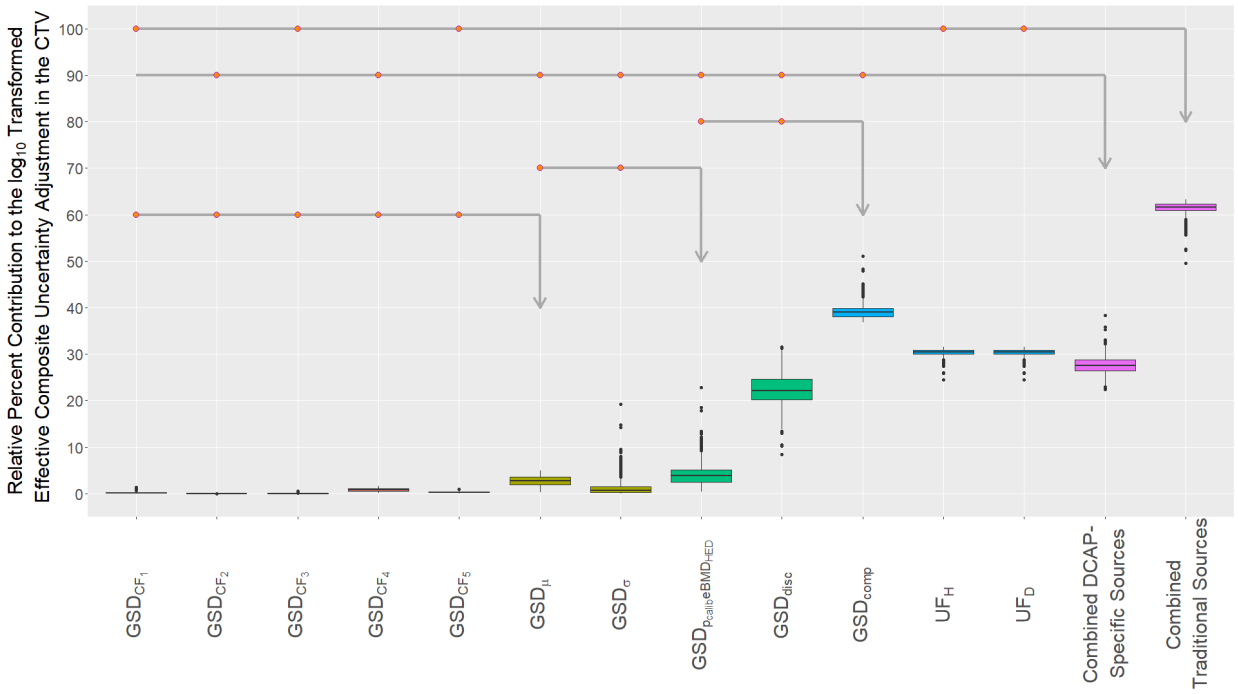


Figure 4-7. Boxplots of relative contributions of uncertainty components considered in the DCAP process to the effective composite uncertainty adjustment in the CTV for the 193 chemicals used in the calibration process. The box represents the inter-quartile range between the 25th and 75th percentiles, while the horizontal line inside the box denotes the median. The whiskers represent the largest (or smallest) observation that is within 1.5 times the interquartile range above Q3 (or below Q1). Observations that fall outside the whiskers are shown individually as dots. Colors of the boxplots are grouped by their tiers of uncertainty adjustment application. The orange dots represent the uncertainty components that constitute the higher-tier uncertainty components indicated by the grey arrow.

4.9. COMPARISON OF CTV VALUES WITH REFERENCE DOSES FROM AUTHORITATIVE SOURCES

To compare the relative level of human health protection afforded by the DCAP, **Figure 4-8** depicts a scatterplot of chronic RfD values from 56 IRIS and 33 PPRTV assessments compared to the corresponding DCAP-derived CTVs for the same chemicals. Based on the cumulative distribution plot, 56% of CTVs fall within an order of magnitude of the RfD values, and 98% of the CTVs fall within two orders of magnitude (**Fig. 4-9**). When compared to all RfD values, 87% of CTV values are lower when compared to the corresponding RfD (*i.e.,* more conservative from a human health standpoint). When comparing separately with IRIS and PPRTVs, 95% of CTV values are lower than IRIS RfDs and 73% are lower than RfD values from PPRTVs. On the arithmetic scale, the median absolute ratio[29] ± median absolute deviation (MAD) between the RfD and CTV values is 7.9 ± 5.5.

[29] The absolute ratio between a and b is defined as maximum{a/b, b/a}.

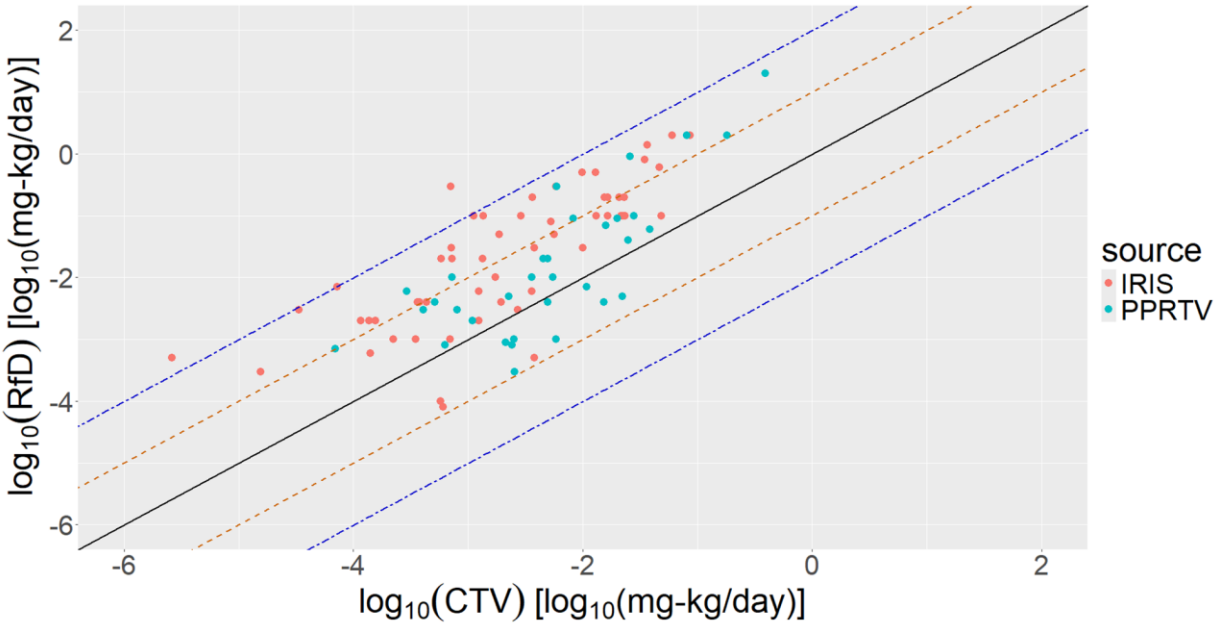


Figure 4-8. A comparison of CTV and RfD values for 89 chemicals from IRIS (red) and PPRTV (blue). The black solid line represents CTV = RfD, while the orange and blue dotted lines represent ± 1 and ± 2 $\log_{10}$ difference, respectively.

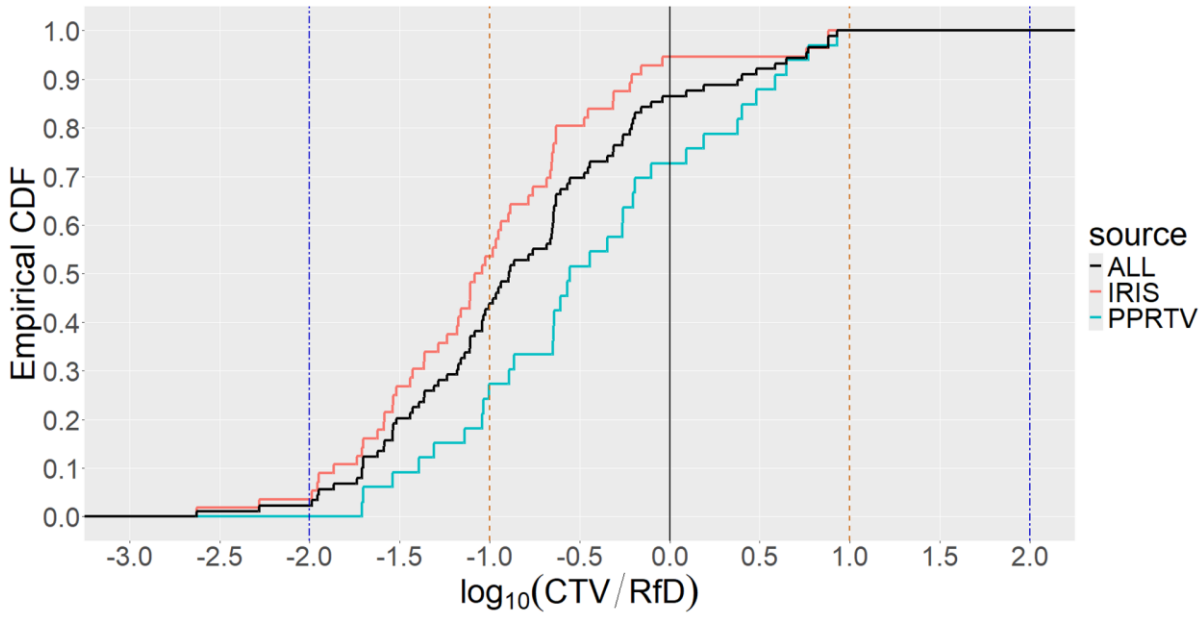


Figure 4-9. A cumulative distribution function (CDF) plot of the CTV-to-RfD ratio for the 89 chemicals from IRIS (red) and PPRTV (blue) assessments. The black vertical solid line represents CTV = RfD, while the orange and blue dotted lines represent ± 1 and ± 2 $\log_{10}$ differences, respectively.

5. DCAP DEMONSTRATION AND IMPLEMENTATION

5.1. OVERVIEW

The DCAP process was developed and characterized using ToxValDB records on 193 authoritative chemicals. To demonstrate application of the DCAP process, ToxValDB records for an additional 8 chemicals were identified. The demonstration chemicals were selected to span a range in the number of consolidated study groups available. The assessment results for each chemical are reported in a standardized template that contains the key information from the DCAP process. Except for the manual QC steps in the ToxValDB record review, the entire process to develop a DCAP is computational to provide scalability, transparency, and reproducibility.

The broader implementation of DCAP will involve the application of the DCAP process to the remaining ToxValDB records that meet the specified information requirements in Sections 2 and 3. The DCAP is intended to be applied to chemicals with publicly accessible *in vivo* repeat-dose toxicity studies from select sources, but lacking expert-derived human health assessments. At the time of this report, the number of total eligible chemicals for development of DCAP toxicity values, based on available information in ToxValDB v9.6.0, is approximately 1,100. The initial implementation of DCAP will be phased in over approximately the course of a year. Releases of DCAPs will be through an EPA website with timing to coincide with multiple factors including QC of the DCAP records, updates to underlying data, and programmatic needs. Due to the highly standardized process and limited expert judgment, the EPA is proposing that the standard method for developing a DCAP is peer reviewed by the EPA BOSC and subject to public comment, while the individual DCAP reports are released to the public without separate peer-review. The proposed peer-review approach is consistent with the EPA Transcriptomic Assessment Product (EPA 2024b). The flowchart outlining the demonstration and implementation of DCAP is provided in **Figure 5-1**.

5.2. DEMONSTRATION OF DCAP

5.2.1. DCAP REPORTING TEMPLATE

The summary results for each chemical are reported in a standardized template that contains the key information from the DCAP process. The information in each DCAP will include the following:

1. A brief background and summary of the DCAP process;
2. Context of use and disclaimer;
3. Description of the review and quality assurance (QA) process;
4. Version of the DCAP and update history;

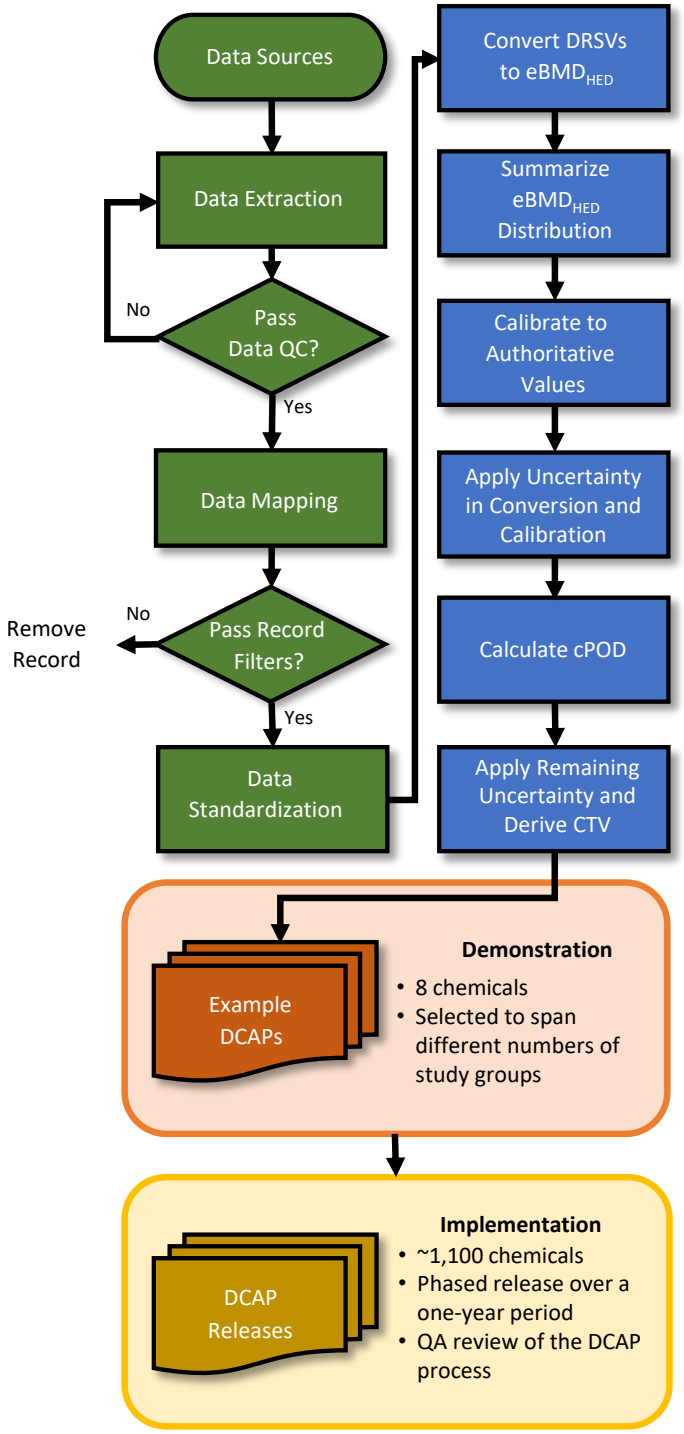


Figure 5-1. Overview flowchart depicting the DCAP process and the demonstration and implementation stages. As described in **Figure 2-4**, the two main components of the DCAP process are: 1) data consolidation and preparation (green); and 2) data conversion, calibration, and uncertainty characterization to derive a CTV (blue). Following the derivation of the CTV, the assessment results for each chemical are reported in a standardized template that contains the key information from the DCAP process. Demonstration of the DCAP is performed on 8 selected chemicals (orange). Implementation will involve the application of the DCAP process to the remaining ToxValDB records that meet the specified information requirements in Sections 2 and 3 (yellow).

5. Identity and physicochemical properties of the chemical if they are calculable (note that the properties for some chemicals may not be calculable);
6. Data sources used;
7. Characteristics of the studies, DRSVs and standardized toxicological effects;
8. Description of the uncertainties in the calibration and calculation of the cPOD; and
9. Derivation of the CTV.

Each assessment is generated as a portable document format (PDF) file using a computationally automated process.

5.2.2. DEMONSTRATION USING SELECT CHEMICALS

To demonstrate application of the DCAP process and reporting template, DCAPs are included for 8 chemicals (**Table 5-1**). The chemicals span a range in the number of studies available: (1) a relatively low number of consolidated study group records (5-10 records); and (2) a larger number of consolidated study group records (>10 records). In addition, a chemical without defined structures or of unknown or variable composition, complex reaction products, or biological materials (UVCB) is provided to demonstrate application to a substance without a defined structure or for which physicochemical properties cannot be readily calculated. The DCAPs for the 8 demonstration chemicals are provided as separate PDF files.

Table 5-1. List of the chemicals selected for demonstrating application of the DCAP process.

DTXSID	CASRN	Chemical Name	Number of Consolidated Study Group Records
DTXSID5020154	120-32-1	Clorophene	22
DTXSID8029600	79-39-0	Methacrylamide	20
DTXSID8024600	56-93-9	Benzyltrimethylammonium chloride	14
DTXSID8052514[a]	7756-94-7	Isobutene trimer	12
DTXSID2020268	115-28-6	Chlorendic acid	9
DTXSID1026118	119-64-2	Tetralin	7
DTXSID9029194	622-96-8	4-Ethyltoluene	7
DTXSID5051234	66204-44-2	3,3'-Methylenebis(5-methyloxazolidine)	7

[a]Chemical without defined structure and UVCB.

5.3. IMPLEMENTATION OF DCAP

5.3.1. ELIGIBLE CHEMICALS

Chemicals that are eligible for development into a DCAP must have DRSVs derived from at least five consolidated study groups.[30] Eligible chemicals must meet the study and exposure characteristics as indicated in Sections 3.2.3 and 3.2.4. In addition, DCAP-eligible chemicals must meet the chemical domain requirements as detailed in Section 3.2. To briefly summarize, eligibility is focused on chemicals of EPA interest (*i.e.,* excluding most drugs and food additives) and those that lack formal, prescriptive testing requirements with corresponding risk assessments (*i.e.,* excluding most pesticides). Exceptions to the exclusion criteria are those drugs, food additives, or pesticides that have multiple functional uses and are registered in the TSCA inventory. Chemicals that have an existing expert-derived human health assessment that is publicly available are not eligible for issuing a DCAP. The total number of eligible chemicals based on available information in ToxValDB v9.6.0 is approximately 1,100.

5.3.2. QUALITY ASSURANCE REVIEW

The DCAP is developed as a stable, repeatable workflow. Based on this intended use, a Technical Systems Audit (TSA) is the most appropriate QA approach. The workflow will be evaluated to ensure that it meets general Agency quality standards for research products. The result of the TSA will be a report that includes a list of best practices, recommendations for improvement, and findings requiring corrective action. Where process improvements are identified, a plan will be created to implement recommendations and to complete corrective actions prior to issuing a DCAP. Upon completion of the TSA and associated corrective actions, the workflow will be certified for repeated use under the existing quality documentation. Any subsequent changes to Agency Quality Standards will trigger a review of the workflow by the Project QA Manager. If the changes are determined to substantially alter the workflow, an additional TSA will be completed to certify the workflow for use under the new quality documentation. This approach has been selected to ensure the direct comparison of independent assessments performed under the same QA documentation. Furthermore, it will document the impact of any substantial changes to the workflow and serve as an aid for comparing results from assessments performed under previous versions of the workflow.

5.3.3. INTERNAL AND EXTERNAL REVIEW

The methods for developing the DCAP outlined in this document have been internally reviewed by ORD scientists and management. A main concept of the DCAP is that the underlying process and data analysis procedures are highly standardized and structured with no expert

[30] Scientific support for determining a minimum of five consolidated study groups for eligibility of DCAP development is included in the Appendix (Section 8.5).

judgment in the calculation of the cPOD or selection of the UFs used to derive the CTV. As a result, the EPA is proposing that the standard method for developing a DCAP be peer reviewed via this document by the EPA BOSC and subject to public comment, while an individual DCAP developed using the method and automated workflow will be publicly released without separate peer-review. The proposed peer-review process is consistent with the EPA Transcriptomic Assessment Product (EPA 2024b). The combination of standardized methods and targeted review process is intended to facilitate the rapid development, execution, and release of a DCAP. If there are major, substantive changes to the DCAP workflow, re-review of the updated process will be sought by the EPA BOSC prior to implementation.

5.3.4. PHASED IMPLEMENTATION AND FUTURE UPDATES

The implementation of DCAP will be phased in over the course of an approximately one-year period to allow for the QC of relevant ToxValDB records and requisite infrastructure to be assembled. Initial batches of DCAPs are anticipated to be released throughout the first year of implementation to a designated EPA website. Following the initial implementation period, ToxValDB may be updated for the selected DCAP sources on a periodic basis depending on available resources. Using the updated ToxValDB data, a DCAP may be issued for any new chemical that meets the specified information requirements in Sections 2 and 3. In addition, a chemical with an existing DCAP for which new information is available may also be updated. Any changes in the assessment will be logged in the version history, and the old DCAP will be retired and archived. If an expert-derived human health assessment from the considered sources is released for a chemical with an existing DCAP, the DCAP will be retired and archived.

The DCAP calibration may also be updated periodically to ensure that the calibration step is using the most up-to-date available information. As part of this process, new DRSV information regarding chemicals used in the calibration step or inclusion of additional chemicals as new human health assessments are published may necessitate re-optimizing the calibration percentile. The process for deriving a re-calibrated optimal percentile will be performed as detailed in Section 4. If recalibration is performed, documentation relating to the methods, data sources, and derivation of the calibration percentile will be published in a document on the EPA website, with an appropriate version number that will be included in any subsequent DCAP. The current version of the calibration, as detailed within this document, is version *calib.1.2024* – for which the first integer will be incrementally increased based on the order of the version (*i.e.* 1st – 1, 2nd – 2, and so on) and the second number will be the year of issuance of the updated calibration percentile.

5.3.5. DATA AND CODE AVAILABILITY

To ensure compliance with Office of Management and Budget (OMB) Mandate M-16-21 *Federal source code policy: Achieving efficiency, transparency, and innovation through reusable and open-source software*, data and source code utilized for the DCAP workflow and assessment development will be posted in publicly available code repositories and databases.

Versioned releases of ToxValDB[31] are made available to the public for download via the US EPA Clowder repository in both XLS and mySQL file formats. The subset of data used to develop DCAP, following the filtering and data standardization steps described in Section 3, is available via EPA Clowder.[32]

The data processing and analysis associated with the DCAP process was performed using the open-source statistical software R. The R code used for importing, processing, and exporting records from ToxValDB can be found in the EPA GitHub repository.[33,34,35] The R code and version utilized for implementing the DCAP workflow will be publicly released following revisions made based on recommendations by the BOSC.

[31] ToxValDB prior version downloads are available at: https://clowder.edap-cluster.com/datasets/61147fefe4b0856fdc65639b#folderId=62e184ebe4b055edffbfc22b

[32] The subset of data used to develop DCAP, following filtering and data standardization is available at: https://figshare.com/s/e591044a660ddb455141

[33] The R-scripts used for importing data into ToxValDB can be found at: https://github.com/USEPA/toxvaldbstage

[34] The R-scripts used to transfer records from the ToxVal Source DB, data mapping and initial standardization, and study group assignment into ToxValDB can be found at: https://github.com/USEPA/toxvaldbmain

[35] The R-scripts used for exporting DCAP records from ToxValDB can be found at: https://github.com/USEPA/toxvaldbBMDh

6. SUMMARY AND CONCLUSIONS

To address the gap in human health assessments for chemicals with human exposure, the EPA is proposing to develop the DCAP as a new addition to the ORD portfolio. The DCAP provides oral, non-cancer CTVs for chemicals using a methods-based approach that is scalable in the development, execution, and release of the assessments. Building on previously published methods (Aurisano et al. 2023; WHO 2018), the DCAP process compiles publicly accessible *in vivo* repeat-dose toxicity studies from select sources, standardizes the data from the studies, and converts the disparate DRSVs into comparable chronic $eBMD_{HED}$ values. The distribution of $eBMD_{HED}$ values is calibrated to PODs for expert-selected critical effects from authoritative sources. The calibration and associated uncertainty are used to calculate a cPOD and derive a CTV. The results from the data compilation, calibration, and CTV derivation are reported in a standard DCAP template using an automated computerized process. Due to the standardized and automated methodology, a streamlined review process is proposed to facilitate the release of the human health assessments. In implementing DCAP, the EPA would apply the method to derive CTV values for approximately 1,100 eligible chemicals.

The CTV is derived from a cPOD with uncertainties incorporated that reflect the limitations of the data used. The cPOD is defined as the lower uncertainty limit of the value associated with the calibrated percentile of a distribution of chronic duration $eBMD_{HED}$ values derived from multiple human health assessment relevant studies. The percentile has been calibrated to PODs for critical effect from select authoritative sources. The median RMSD measuring concordance between the calibrated percentile from the distribution of $eBMD_{HED}$ values and the $eBMD_{HED}$ corresponding to the expert-selected critical effect, underlying published RfD values, is 0.614 with lower 5^{th} and upper 95^{th} percentiles of 0.504 and 0.701, respectively. The RMSD accounts for multiple sources of variability contributing to the error in the prediction process, including not only interstudy variability, but also variability in identification of authoritative values and systematic error in the calibration. The median RMSD is only slightly larger than the reported range of interstudy standard deviation estimates of LOAELs from multiple repeat dose studies for systemic toxicity, approximated as residual root mean square error (RMSE) in log_{10}-mg/kg-day units [0.448-0.559; (Pham et al. 2020)]. The similarity in magnitude of both the median and lower 5^{th} percentile concordance RMSD values to the range of RMSE values estimating interstudy variability of LOAEL values suggests that interstudy variability may comprise a substantial portion of the error associated with the calibration process and that the selection of the correct percentile may add only a small amount of variability to the interstudy variability in the repeat dose toxicity study from which an expert selects the critical effect. Notably, the five types of uncertainty incorporated in traditional human health assessments do not expressly account for the potential interstudy variability in the toxicity studies from which the critical effect is selected. However, interstudy variability is considered in the DCAP via the GSD_{disc}, associated with

the RMSD (and its uncertainty) which inherently accounts for interstudy variability across the set of authoritative chemicals as a source of error. The advantage of incorporating this uncertainty in the DCAP process is that it allows for quantification of the inherent limitations in the underlying data available for the systematic process used to derive a CTV.

The formal statistical optimization and evaluation during the calibration process is primarily focused on the $eBMD_{HED}$ values. However, because reference values are ultimately used in decision making, a comparison of available traditional RfD and CTV values provides some understanding of the relative level of health protection afforded by the DCAP process. Using the cPOD and proposed UF_H and UF_D values of 10, the median absolute ratio ± MAD between the RfD and CTV values is 7.9 $\pm$ 5.5 on the arithmetic scale. When compared to all RfD values, nearly 87% of corresponding CTV values are lower when compared to the corresponding RfD (*i.e.,* conservative from a human health standpoint). When comparing separately with IRIS and PPRTVs, 95% of CTV values are lower than IRIS RfD values and 73% are lower than RfD values from PPRTVs. The conservatism in the CTV values is primarily due to the incorporation of a larger composite uncertainty. A comparison of the ECUA from the CTVs and the composite UFs from IRIS and PPRTVs show that the median composite uncertainty is approximately 76% higher in DCAP. However, the relative contributions of the uncertainties in DCAP shows that when evaluating only the five sources of uncertainty considered in the traditional risk assessment, these uncertainties contribute approximately 50 – 63% of the adjustment expressed on the log-scale.

An alternative approach to the UF_D value was also considered and presented in the Appendix. Using the cPOD, a UF_H of 10, and the alternative UF_D that varied depending on the composition of study groups, the median absolute ratio ± MAD between the RfD and CTV values is 4.4 $\pm$ 3.0 on the arithmetic scale. While showing closer overall alignment with the RfD values, approximately 73% of corresponding CTV values are lower when compared to the corresponding RfD (*i.e.,* conservative from a human health standpoint). When comparing separately with IRIS and PPRTVs, 82% of CTV values are lower than IRIS RfD values and 58% are lower than RfD values from PPRTVs. The lower conservatism in the CTV values associated with the alternative UF_D approach is due to the incorporation of a lower median composite uncertainty in DCAP. When evaluating only the five sources of uncertainty considered in the traditional risk assessment, these uncertainties contribute approximately 45 – 65% of the adjustment expressed on the log-scale. Overall, the results suggest that the CTV using the cPOD and proposed UF_H and UF_D values of 10 provides a comparable, conservative level of protection relative to the IRIS and PPRTV RfD values that is appropriate for the intended application to chemicals with *in vivo* toxicity testing data, but without an expert-derived human health assessment.

Demonstration of the DCAP process is illustrated using a subset of chemicals that are selected based on differences in the number of study groups available for the chemical as well as several chemicals without a defined structure or UVCBs. A large percentage of the chemicals registered under TSCA are UVCBs (Lai et al. 2022), and given the intended chemical domain covered by DCAP, it is

important to incorporate these types of substances into the process. The key results of the DCAP process for each chemical are reported in a standardized DCAP template that is automatically generated as a PDF file.

The initial implementation of DCAP will be phased in over the course of approximately one year with batches of assessments anticipated to be released on an approximate quarterly basis. The phased approach allows manual QC of the relevant ToxValDB records, QA audit of the DCAP process, and the development of the infrastructure to accommodate the new human health assessment product. Depending on available resources, ToxValDB may be updated for the selected DCAP sources on a periodic basis. A new DCAP may be issued for any new chemicals meeting the information requirements while an existing DCAPs may be updated if new data is available. If an expert-derived, authoritative human health assessment is released on a chemical with a DCAP, the DCAP will be retired and archived. Periodically, the DCAP calibration may also be updated to ensure that the calibration step is using the most up-to-date available information.

There are several potential caveats in the application of the DCAP process to develop CTVs for decision-making. First, the cPOD is not necessarily associated with a specific hazard or adverse effect as expected in a traditional expert-derived human health assessment. Rather, the cPOD is defined as the lower uncertainty limit of the value associated with the calibrated percentile of a distribution of chronic $eBMD_{HED}$ values derived from multiple human health relevant studies that may include a range of potential effects. Although the specific percentile is calibrated to the PODs for critical effects from expert developed human health assessments, the $eBMD_{HED}$ value at the percentile is not ascribed to a specific endpoint of concern. Second, the DRSVs and associated studies that are used to develop the distribution of $eBMD_{HED}$ values have not undergone a formal confidence evaluation. Although the DCAP relies on a select subset of more reliable sources in ToxValDB, some of the sources incorporate user-submitted data and studies. For example, the ECHA data encompasses industry-developed dossiers submitted under the Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) regulation. Although the calibration process reduces the potential impact of any single source since they are incorporated into the $eBMD_{HED}$ distribution for the authoritative chemicals used in the calibration, the specific studies have not been reviewed as part of a formal confidence evaluation. Third, the methodology used to estimate the uncertainties for UF_S (*i.e.,* uncertainty in extrapolating from shorter-duration studies to chronic duration), UF_L (*i.e.,* uncertainty in extrapolating from a LOAEL to a NOAEL), and UF_A (*i.e.,* uncertainty in extrapolating from an animal to a human) do not follow standard EPA practice. In current EPA human health assessments, in the absence of chemical-specific data supporting quantitative application of uncertainty, standard UFs of 10 are recommended, with 3 used in place of half-power values (*i.e.*, $10^{0.5}$) if some aspect of uncertainty is accounted for, or if uncertainty is not comprehensively addressed. A UF of 1 is applied if either the uncertainty is not relevant or if qualitative evidence comprehensively characterizes an area of uncertainty. In DCAP, the uncertainties associated with UF_S, UF_L, and UF_A are calculated based on the WHO/IPCS guidance that

is used to convert the DRSV into chronic $eBMD_{HED}$ values (WHO 2018). Although different in practice, the uncertainty is accounted for in a statistically rigorous manner. Finally, while DCAP builds on the previous work of Aurisano et al., Chiu et al., and the WHO/IPCS guidance which are expressly probabilistic (Aurisano et al. 2023; Chiu et al. 2018; WHO 2018), the CTV is currently a deterministic value. The choice of a deterministic CTV was informed by the extent of current EPA policies and processes that utilize deterministic assessments and the associated toxicity values. The DCAP process is compatible with developing a probabilistic CTV and can be modified as EPA policies and processes evolve to utilize probabilistic assessments.

In summary, human health assessments are foundational to informing federal, state, and local decisions on chemicals. However, the time and resources required to develop and release a traditional, expert-derived human health assessment are not compatible with the thousands of chemicals to which the US population is exposed. The EPA ORD has developed the DCAP to fill a niche in its human health assessment portfolio to provide timely toxicity values for chemicals that have *in vivo* toxicity testing data from select EPA and non-EPA sources but lack expert-derived human health assessments. Implementation of the DCAP would nearly triple the number of human health assessments available to program offices, states, communities, and tribes. The scalable generation of toxicity values for chemicals that lack human health assessments would likely have significant economic and human health benefits based on previous socio-economic analyses (EPA 2024c; Hagiwara et al. 2022). While there are acknowledged caveats associated with the DCAP process, the overall benefits of the DCAP to provide timely, transparent, and scalable human health assessments outweigh the potential limitations and support its use to inform decision making.

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8. APPENDIX

8.1. ACCESS DETAILS ON INFORMATION SOURCES IN TOXVALDB USED IN DCAP

The accession details of the information sources in ToxValDB 9.6.0 used in DCAP are provided in **Table 8-1**.

Table 8-1. Information sources in ToxValDB used in DCAP

ToxValDB Information Source	Access Link(s)	Access Date for ToxValDB Version 9.6.0
Agency for Toxic Substances and Disease Registry (ATSDR)	https://wwwn.cdc.gov/TSP/MRLS/mrlsListing.aspx	Jan 2024
	https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=1117&tid=237	May 2021
California OEHHA	https://oehha.ca.gov/chemicals	Aug 2023
European Chemicals Agency (ECHA)	https://iuclid6.echa.europa.eu/en/get-iuclid-data	Aug 2023
European Food Safety Authority (EFSA) OpenFoodTox	https://zenodo.org/record/5076033#.Y9fEoXbMI2z	Jun 2022
Health Canada	https://publications.gc.ca/site/eng/9.694269/publication.html	Sep 2010
Japan's National Institute of Technology and Evaluation (NITE)	https://www.nite.go.jp/en/chem/qsar/hess_01-e.html	Jun 2021
National Toxicology Program (NTP)	https://ntp.niehs.nih.gov/whatwestudy/topics/pfas#studies	Jul 2023
Health Assessment Workplace Collaborative (HAWC) Project	https://hawcproject.org/	Dec 2021
World Health Organization (WHO) Joint Expert Committee on Food Additives (JECFA)	https://apps.who.int/food-additives-contaminants-jecfa-database/	Nov 2022
EPA EcoTox Knowledgebase (ECOTOX)	https://cfpub.epa.gov/ecotox/	Sep 2024
EPA Health Assessment Workplace Collaborative (HAWC)	https://hawc.epa.gov/	Jun 2021
EPA High Production Volume Information System (HPVIS)	https://chemview.epa.gov/chemview/	Dec 2019
EPA Toxicity Reference Database (ToxRefDB)	https://doi.org/10.23645/epacomptox.6062545.v4	Apr 2024
EPA Human Health Toxicity Values (HHTV)	• https://cfpub.epa.gov/si/si_public_record_Report.cfm?Lab=CPHEA&dirEntryId=358291 • https://assessments.epa.gov/risk/document/&deid%3D358288#overview	Jun 2024

Table 8-1. Information sources in ToxValDB used in DCAP		
	• https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=350888 • https://www.epa.gov/system/files/documents/2024-05/final-human-health-toxicity-assessment-pfoa.pdf • https://www.epa.gov/system/files/documents/2024-05/final-human-health-toxicity-assessment-pfos.pdf	
EPA Health Effects Assessment Summary Tables (HEAST)	https://assessments.epa.gov/risk/document/&deid=2877	Jul 1997
EPA Integrated Risk Information System (IRIS)	https://iris.epa.gov/AtoZ/?list_type=alpha	May 2023
EPA Provisional Peer-Reviewed Toxicity Values (PPRTV)	https://www.epa.gov/pprtv/provisional-peer-reviewed-toxicity-values-pprtvs-assessments	Jun 2024

8.2. ASSIGNMENT OF STANDARD TOXICOLOGICAL EFFECT CATEGORIES

Dose-effect linkage information within ToxValDB is derived from a number of information sources with no standardized vocabulary or rules for describing the endpoints observed. A key step in the DCAP process requires the conversion of the DRSVs to $eBMD_{HED}$ values. The conversion process requires the assignment of standardized toxicological effect categories that allows the fit of a conceptual mathematical model as described previously (Aurisano et al. 2023; WHO 2018). The assignment of the standardized toxicological effect categories is performed by a team of EPA toxicologists. The non-standardized toxicological effect descriptions are randomly assigned to two independent reviewers. Each reviewer groups the reported toxicological effects into one of the standardized categories. To facilitate assignment of the non-standardized toxicological effect descriptions into the standardized toxicological effect categories, an assignment rubric is provided in **Table 8-2**.

Table 8-2. Standard toxicological effect category descriptions.		
Standard Toxicological Effect Category	**Included Effects**	**Excluded Effects**
Body weight	Changes in body weight	Fetal or pup weight changes less than PND 22 were designated as developmental
Cancer[1]	Blood cancers, tumor findings, designation of metaplastic, histopathological findings of '-omas'	Microgranuloma, granuloma, and metaplasia were designated as nonneoplastic histopathology
Clinical chemistry	Standard clinical chemistry measures and circulating hormone levels	
Clinical signs	Cage side observations, behavior changes not associated with intentionally measured functional observation battery, gross	Purposefully measured behavior was designated as neurobehavior

Table 8-2. Standard toxicological effect category descriptions.		
	observations in teeth or oral mucosa, cardiac function tests, neurophysiological tests	
Developmental	Any change in the fetus or pup younger than PND 22, changes related to developmental milestones or developmental malformations at any age	
Enzyme activity	Quantitative measurements of enzyme abundance or activity	Excludes circulating enzyme measures that are part of a standard clinical chemistry panel
Gross pathology	Macroscopic manifestations of disease in organs, tissues, and body cavities; Measurements of tissues using imaging studies (CT, MRI, DEXA)	
Hematology	Standard hematology measures	Circulating immunoglobulin and cytokine measurements were designated as other
Mortality/survival	Adult or juvenile mortality or survival measures (≥PND 22)	Mortality or survival of the developing fetus or pup at birth (PND 0) was designated as reproductive; Mortality or survival of pups between PND 1 and PND 22 were designated as developmental
Neurobehavior	Purposely measured neurobehavioral measures using a variety of behavioral testing apparatus or a functional observation battery	
Neurotransmitter	Activity of neurotransmitter enzymes in either circulation or in tissues	
Nonneoplastic histopathology	Macroscopic manifestations of disease in organs or tissues of the body; When organ toxicity was specified, but the measurement method was not indicated, the effect was designated as nonneoplastic histopathology	Findings associated with the cancer standard effect were designated as cancer[1]
None	The standard effect category of 'none' was assigned to DRSVs associated with the NOAEL, NOEL, or NEL	
Organ weight	Changes in organ weights or organ-to-body weight ratio	
Other	Included effects that were not easily captured in alternative standard effect categories. Effects designated as other included gene transcription, cytokine or antibody measurements, tissue glutathione and oxidative stress marker measurements, cellularity measures in tissues via immunohistochemistry, cellularity measures in blood via flow cytometry, vitamin measurements in blood	Cellularity measures in blood that are included in standard hematological analysis were designated as hematology

Table 8-2. Standard toxicological effect category descriptions.		
Reproductive	Sexual behavior measures, pregnancy or implantation success rates, measures of sperm abundance or quality, lactation or nursing parameters, placenta size or quality measures	*In situ* analysis of histological or cellular measures in sex organs, such as spermatid formation or estrous cycle parameters were designated as nonneoplastic histopathology
Urinalysis	Standard urinalysis measures	
[1]Findings associated with the cancer standard effect category are considered outside of the domain of applicability for DCAP and excluded from analysis. NA: not applicable, PND: postnatal day, CT: computed tomography, MRI: magnetic resonance imaging, DEXA: dual-energy X-ray absorptiometry.		

8.3. ASSIGNMENT OF CONCEPTUAL MATHEMATICAL MODELS

Conceptual mathematical models are used to convert DRSVs to $eBMD_{HED}$ values based on standardized study type and toxicological effect. Conceptual mathematical models are assigned as follows: 1) continuous is designated for continuous endpoints; 2) quantal-stochastic is designated for effects where the dose-response relationship represents an individual probability of developing the endpoint (*e.g.,* malformations); and 3) quantal-deterministic is designated for effects where the dose-response relationship represents experimental variation (*e.g.,* histological findings). The assignment of the conceptual mathematical model with the standardized study type and standardized toxicological effect is consistent with previous work and outlined in **Table 8-3** (Aurisano et al. 2023; WHO 2018).

Table 8-3. Linkage of study type and standardized toxicological effect to conceptual mathematical model used to convert DRSV to $eBMD_{HED}$ values.

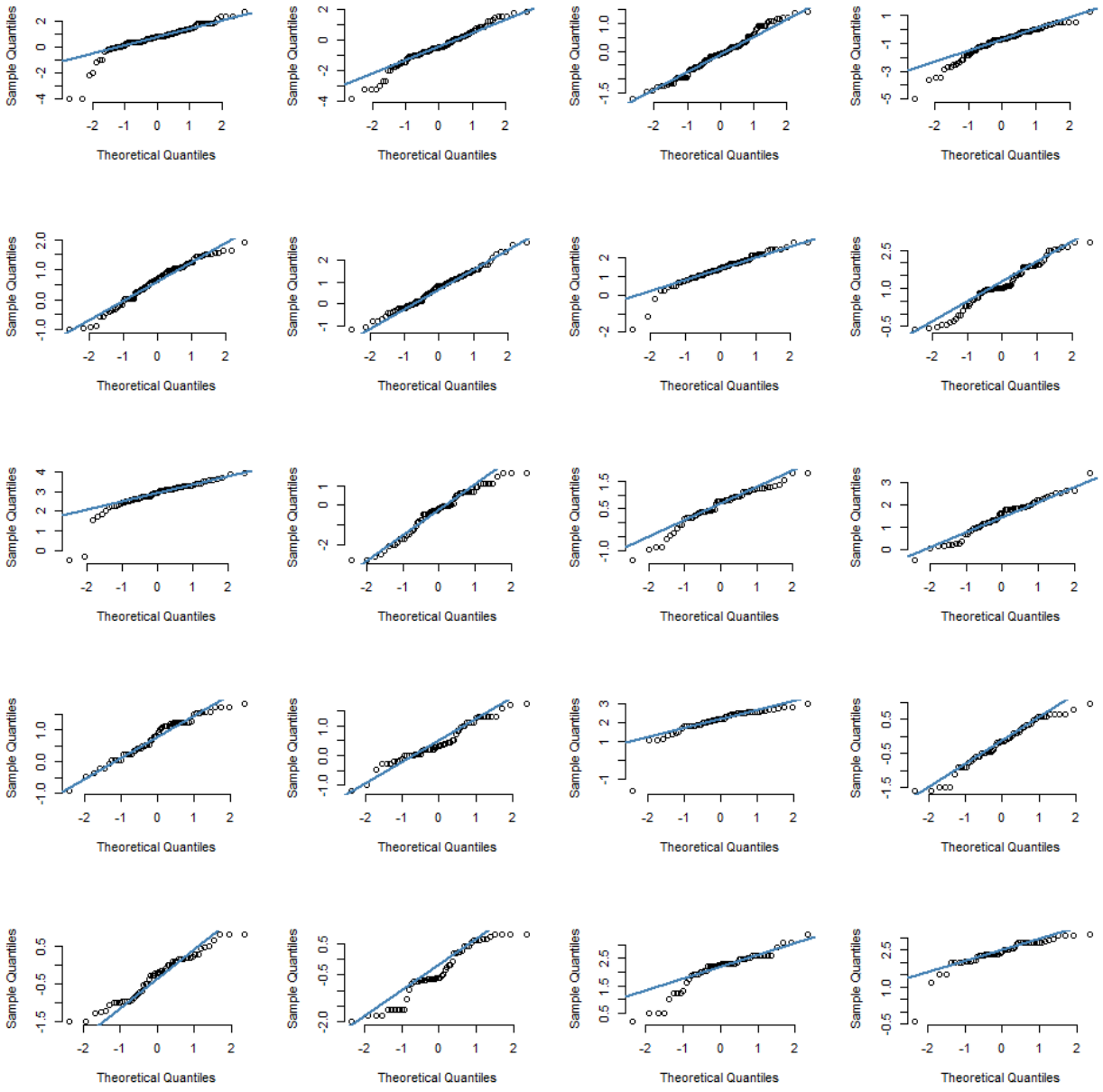
Standardized Study Type	Standardized Toxicological Effect	Conceptual Models[d] (Model 1 / Model 2)
Repeat dose/ reproductive developmental	Body weight	Continuous / -
Repeat dose/ reproductive developmental	Clinical chemistry	Continuous / -
Repeat dose/ reproductive developmental	Enzyme activity	Continuous / -
Repeat dose/ reproductive developmental	Food and/or water consumption	Continuous / -
Repeat dose/ reproductive developmental	Hematology	Continuous / -
Repeat dose/ reproductive developmental	Neurotransmitter	Continuous / -
Repeat dose/ reproductive developmental	Organ weight	Continuous / -
Repeat dose/ reproductive developmental	Urinalysis	Continuous / -
Repeat dose/ reproductive developmental	Clinical signs	Quantal-Deterministic / -

Repeat dose/ reproductive developmental	Gross pathology	Quantal-Deterministic / -
Repeat dose/ reproductive developmental	Mortality/survival	Quantal-Stochastic / -
Repeat dose/ reproductive developmental	Nonneoplastic histopathology	Quantal-Deterministic / -
Repeat dose/ reproductive developmental	Neurobehaviour	Continuous / Quantal-Deterministic
Repeat dose	Multiple[a]	Continuous / Quantal-Deterministic
Repeat dose	None[b]	Continuous / Quantal-Deterministic
Repeat dose	Other[c]	Continuous / Quantal-Deterministic
Reproductive developmental	Development	Continuous / Quantal-Stochastic
Reproductive developmental	Reproduction	Continuous / Quantal-Stochastic
Reproductive developmental	Multiple[a]	Continuous / Quantal-Stochastic
Reproductive developmental	None[b]	Continuous / Quantal-Stochastic
Reproductive developmental	Other[c]	Continuous / Quantal-Stochastic

[a]For records with more than one unique endpoint category (*e.g.,* effects reported within body weight, clinical chemistry, and clinical signs for the same study group), models corresponding to the standardized endpoint category "multiple" were assigned. [b]The effect category associated with the NOAEL or NEL was indicated as "none". [c]Effects associated with an endpoint category beyond those indicated in the table were assigned as "other". [d]Per the WHO/IPCS guidance, continuous is designated for continuous endpoints, quantal-stochastic is designated for effects where the dose-response relationship represents an individual probability of developing the endpoint, and quantal-deterministic is designated for effects where the dose-response relationship represents experimental variation (*e.g.* histological findings).

8.4. ASSUMPTION OF LOGNORMALITY FOR THE DISTRIBUTION OF $eBMD_{HED}$ VALUES

As discussed in Section 4.2, a lognormal distribution is fit to the $eBMD_{HED}$ values for each chemical eligible for inclusion in DCAP. **Figure 8-1** shows 25 normal quantile-quantile plots for the $\log_{10}(eBMD_{HED})$ values for chemicals with at least 30 unique $eBMD_{HED}$ values. Visual inspection of these plots provides support for the assumption of lognormality for the distribution of $eBMD_{HED}$ values. This is particularly true in the central part of the distribution (between ± 1 standard deviations from the mean on the $\log_{10}$-scale). The optimal calibration percentile, p_{calib}, which is determined to be the 18th percentile, is 0.9 standard deviation below the center of the assumed lognormal distribution.


Sample Quantiles
Theoretical Quantiles

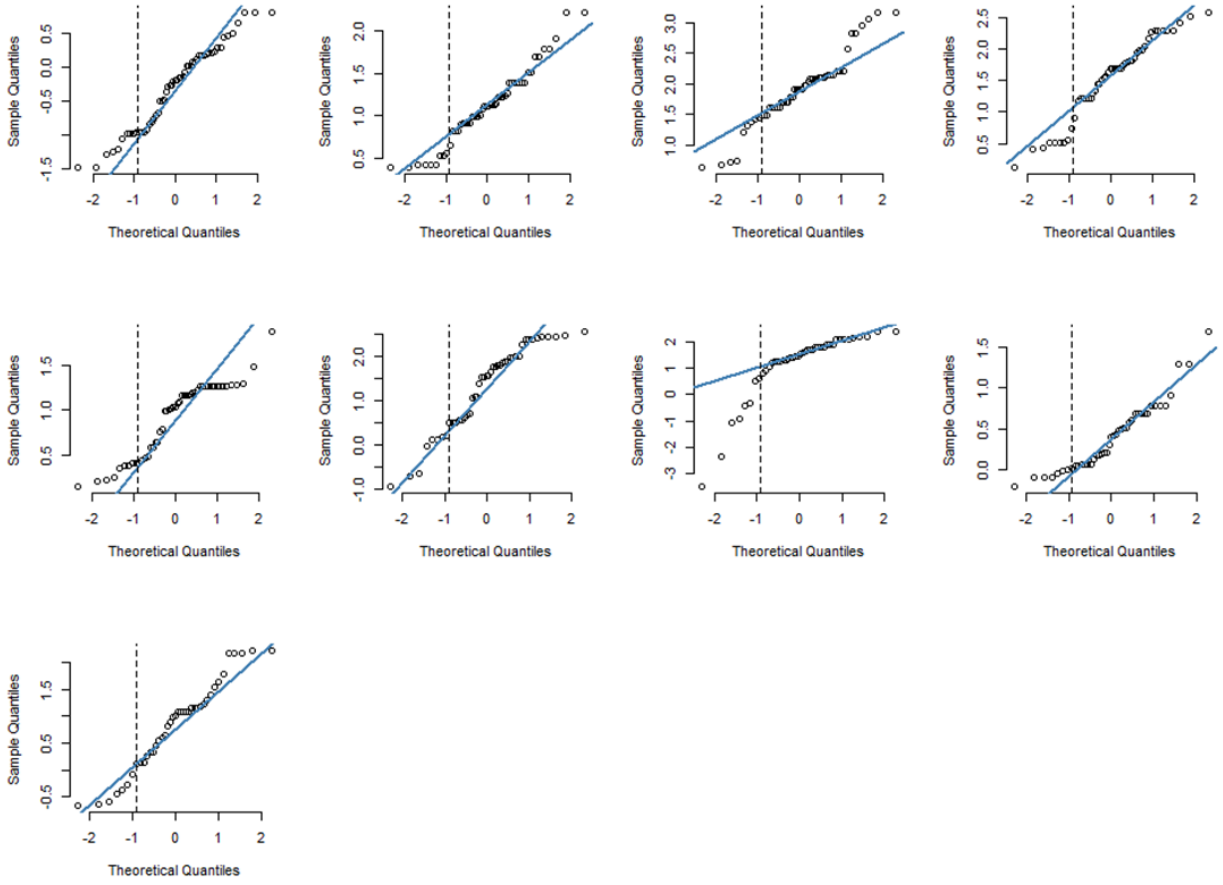


Figure 8-1 (continued). Quantile-quantile plots of for the $\mathbf{log_{10}}(\mathrm{eBMD_{HED}})$ values for chemicals with at least 30 unique $\mathrm{eBMD_{HED}}$ values. The dashed vertical line represents where the calibrated percentile falls in the distribution.

8.5. ANALYSES SUPPORTING THE MINIMUM NUMBER OF CONSOLIDATED STUDY GROUPS REQUIRED FOR DCAP PROCESS

Although it is theoretically possible to derive CTVs for chemicals with as few as two DRSVs, this may not be advisable due to the potentially large uncertainty in the estimation of the DCAP parameters that define the CTV. **Figure 8-2** displays the boxplots of $\log_{10}\left(\mathrm{GSD}_{p_{\mathrm{calib}}\mathrm{eBMD}_{\mathrm{HED}}}\right)$ values according to the number of consolidated study groups available, each with its preferred DRSVs. As seen in Panel A, the values of $\log_{10}\left(\mathrm{GSD}_{p_{\mathrm{calib}}\mathrm{eBMD}_{\mathrm{HED}}}\right)$ when the number of consolidated study groups is two are often excessive, spanning in some cases close to 20 orders of magnitude. As seen in Panel B, increasing the number of consolidated study groups to three or four dramatically reduces this uncertainty, but still includes values spanning three or more orders of magnitude. Panel B also indicates that the uncertainty is further reduced as the number of consolidated study groups increases, with the maximum $\log_{10}\left(\mathrm{GSD}_{p_{\mathrm{calib}}\mathrm{eBMD}_{\mathrm{HED}}}\right)$ when the number of consolidated study

groups is five approaching slightly more than one order of magnitude. These sensitivity analyses provide further quantitative support for the restriction that CTVs are only calculated for chemicals when there are at least five consolidated study groups.

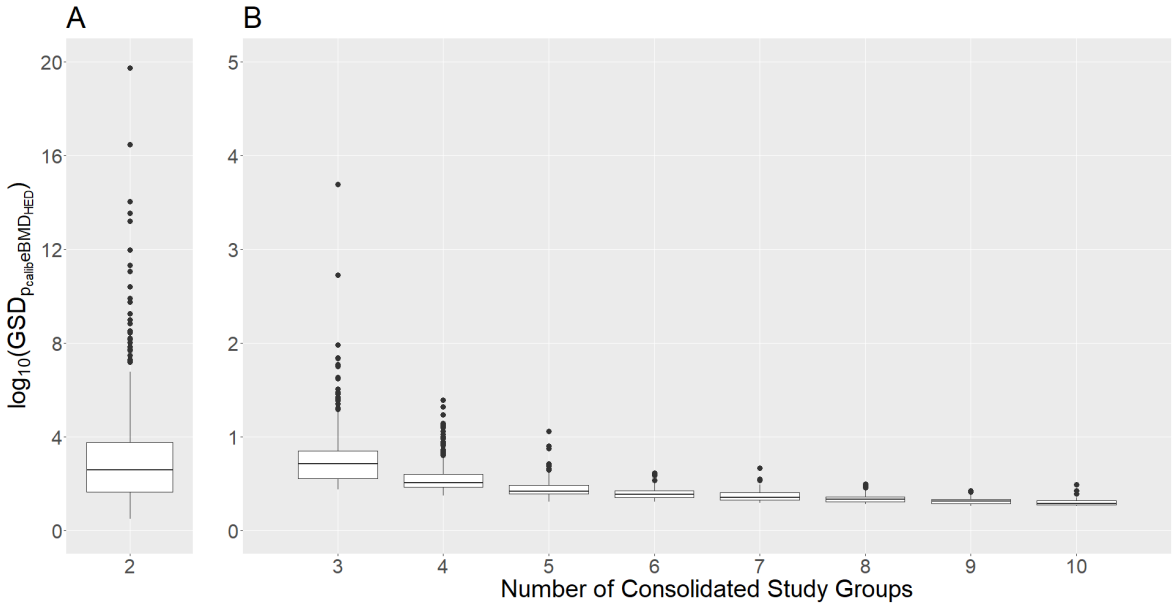


Figure 8-2. Boxplots of $\mathrm{GSD}_{p_{\mathrm{calib}}\mathrm{eBMD}_{\mathrm{HED}}}$ values stratified by the number of consolidated study groups, each with a preferred DRSVs. Results for chemicals with two consolidated study groups shown in Panel A reflect the extreme variation in these values. In Panel B, results for chemicals with three to 10 consolidated study groups reflect markedly less variation, with results for five or more consolidated study groups showing modest variation spanning about one order of magnitude.

8.6. EFFECT OF CHOOSING DIFFERENT SPLITS FOR CROSS-VALIDATION

In conducting cross-validation, consideration needs to be given to the size of the split between the first dataset, called the training dataset, and the second dataset, called the testing dataset. Although a 50-50 split between the training and testing sets is commonly used in practice, other splits with larger training sets (*e.g.,* 70-30 and 90-10) are also used, depending on the application. To investigate the impact of the relative sizes of the training and testing datasets, the following possible splits were considered: 50-50, 60-40, 70-30, 80-20, and 90-10. The distributions of the optimal calibration percentile, p_{calib} and corresponding RMSD values are estimated for these five splits as shown in **Figure 8-3**. Histograms on the left-hand side depict the variation in the estimated values of p_{calib} obtained by randomly repeating the cross-validation 10,000 times. As the proportion of data included in the training data increases, the estimated values p_{calib} becomes more homogeneous. On the other hand, assigning a larger proportion of data to the training set results in a reduced number of chemicals being used in the derivation of the RMSD. This results in greater variability in the distribution of RMSD values, which in turn leads to a less stable estimate of the $\mathrm{GSD}_{\mathrm{disc}}$, defined as the upper 95$^{\mathrm{th}}$ percentile on 10^{RMSD}. Based on these results, splitting the data equally between the

training and testing datasets (*i.e.,* 50-50 split) produces stable estimates for both p_{calib} and RMSD. **Table 8-4** shows the values of GSD_{disc} for the five splits considered here and the unsplit data for comparison. The use of unsplit data is not recommended as it may lead to underestimation of the GSD_{disc} due to the lack of independence between the training and testing set. Nonetheless, the comparison to unsplit data is informative, as it represents a lower bound on the minimum value of GSD_{disc} that can be obtained using various cross-validation splits. Using a 50-50 split, $\text{GSD}_{\text{disc}} = 5.0$, approximately 25% greater than the value of $\text{GSD}_{\text{disc}} = 4.0$ (inappropriately) derived using the entire dataset for both training and validation.

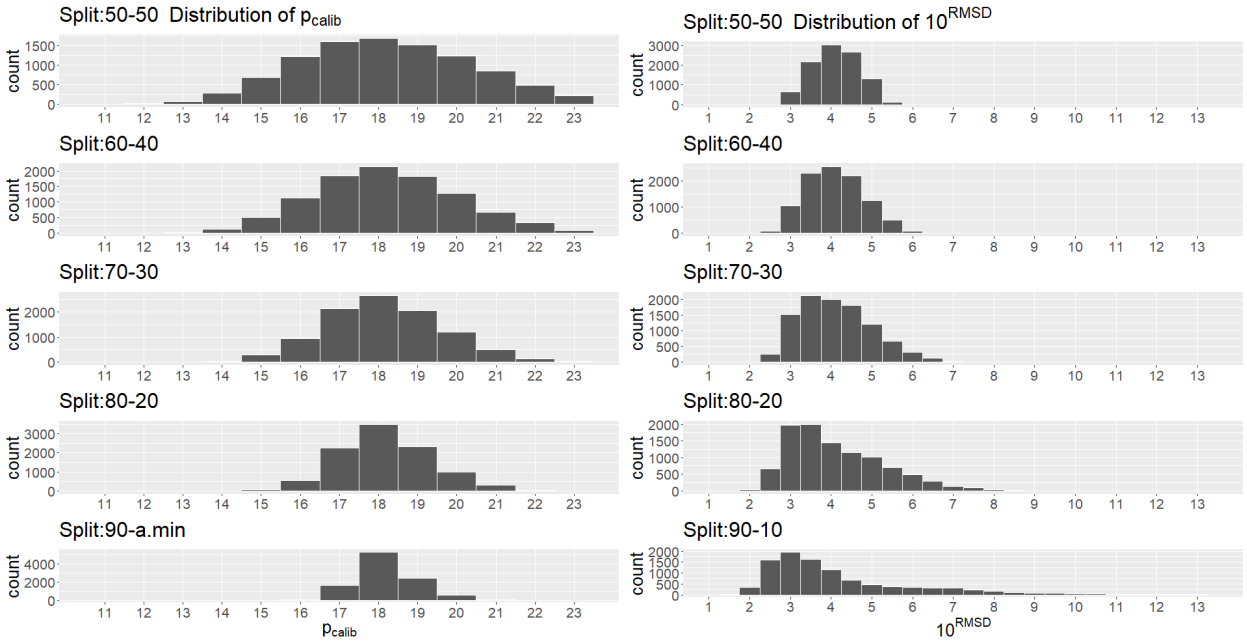


Figure 8-3. Histograms of p_{calib} values generated using 10,000 iterations of cross-validations (left). Histograms of 10^{RMSD} values corresponding to the 10,000 iterations of cross-validations (right). For each iteration, the 193 chemicals used in the calibration step are split into training set (50, 60, 70, 80, and 90%) and testing set (50, 40, 30, 20, and 10%).

Table 8-4. Estimated median, 5th, and 95th percentiles of the 10^{RMSD} values derived using 10,000 cross-validation for different splits in the cross-validation.

Split for Cross-Validation (% training – % testing)	Estimated Median 10^{RMSD}	Estimated Lower 5th Percentile of 10^{RMSD}	Estimated GSD_{disc} (Upper 95th Percentile of 10^{RMSD})
All data (no split)[a]	4.0	4.0	4.0
50-50	4.1	3.2	5.0
60-40	4.1	3.1	5.3
70-30	4.0	2.9	5.7
80-20	3.9	2.7	6.4
90-10	3.6	2.3	8.0

[a] Results shown for reference only. To estimate the RMSD accurately, the testing set needs to be independent of the training set.

8.7. EVALUATING THE APPLICATION OF AN ALTERNATIVE DATABASE UNCERTAINTY FACTOR

8.7.1. DEVELOPMENT OF THE ALTERNATIVE DATABASE UNCERTAINTY FACTOR

The UF_D aims to address the possibility of establishing an insufficiently protective reference value due to an incomplete understanding of the chemical's toxicity. In considering the application of the UF_D, the Agency considers both the data lacking and the data available for health outcome domains, tissues, organ systems, and life stages (EPA 2000) as well as the degree of confidence in the studies (EPA 2022). In the main body of the report, a UF_D of 10 is applied universally to all chemicals due to the presumption of low confidence for the studies forming the basis of the $eBMD_{HED}$ value distribution and potential data gaps in the underlying toxicity database. As an alternative to applying a UF_D of 10 to all chemicals, an approach was considered that:

- Applies a UF_D = 3 to chemicals that had $\geq$ 1 repeat dose consolidated study groups AND $\geq$ 1 reproductive-developmental consolidated study groups.
- Applies a UF_D = 10 to all other remaining chemicals.

Although no formal confidence assessment is conducted on the studies forming the basis of the $eBMD_{HED}$ value distribution, the requirement of both repeat dose and developmental-reproductive consolidated study groups addresses potential data gaps in health outcome domains in the underlying toxicity database.

8.7.2. DERIVATION OF CALIBRATED TOXICITY VALUE USING THE ALTERNATIVE DATABASE UNCERTAINTY FACTOR

Using the cPOD defined by Eq. (18), the value of the CTV using the alternative UF_D can be derived based on the following equation:

$$\text{CTV} = \frac{\text{cPOD}}{\text{UF}_\text{A}^* \times \text{UF}_\text{S}^* \times \text{UF}_\text{L}^* \times \text{UF}_\text{H}\,(10) \times \text{UF}_\text{D}\,(3 \text{ or } 10)} = \frac{\text{cPOD}}{30 \text{ or } 100}\,. \qquad (23)$$

The UF_A, UF_S, and UF_L are labeled with an asterisk to denote that these uncertainties are incorporated upstream in the workflow when calculating the cPOD (and each has the value of 1 for the purpose of Eq. 23). The UF_H has a default value of 10. The UF_D is 3 for chemicals with both a repeat dose and a reproductive-developmental consolidated study group included in the $eBMD_{HED}$ value distribution. The UF_D is 10 for chemicals that do not have both a repeat dose and a reproductive-developmental consolidated study group in the $eBMD_{HED}$ value distribution.

8.7.3. EFFECTIVE COMPOSITE UNCERTAINTY ADJUSTMENT USING THE ALTERNATIVE DATABASE UNCERTAINTY FACTOR

The use of the alternative UF_D in the derivation of the CTV impacts the overall summary statistics for the ECUA as well as the relative contributions among the different components of the composite uncertainty. Among the 193 chemicals with authoritative toxicity values included in the calibration step, a total of 89 have either IRIS or PPRTV RfD values. **Table 8-5** provides the summary statistics of composite UF applied to derive the 89 IRIS and PPRTV RfD values, as well as the ECUA values in DCAP with the alternative UF_D approach. The overall range of the ECUA values with the alternative UF_D approach is approximately 1.4-fold larger than that observed with a default UF_D of 10 (**Table 4-3**). The median ECUA value for DCAP is approximately half of the median composite UF values for IRIS and PPRTV (531 vs. 1,000), while the 25th percentile value is 1.6- to 4.9-fold higher for DCAP (491 vs. 300 or 100). The 75th percentile value for DCAP (706) is 0.7-fold lower than IRIS (1,000) and 4.2-fold lower than PPRTV (3,000).

Table 8-5. Summary statistics of the composite UFs and corresponding EUCA values using the alternative UF_D for IRIS and PPRTV chemicals used in the calibration process.

Data source	*n*	Min.	25%	Median	75%	Max.
IRIS ($UF_{composite}$)	56	3	100	1,000	1,000	10,000
PPRTV ($UF_{composite}$)	33	30	300	1,000	3,000	3,000
DCAP (ECUA)	89	440	491	531	706	2,409

The relative percent contribution associated with each component of the ECUA across the 193 chemicals used in the calibration process is provided in **Figure 8-4**. As expected, the relative contributions of the UF_D and the 'Combined Traditional Sources' that includes the UF_D are lower with the alternative approach, while the relative contributions for the other sources of uncertainty increase. However, the overall impact of the alternative UF_D approach is small on a relative basis with the UF_D reduced from approximately 30% to less than 20% on a log-scale and the 'Combined Traditional Sources' is reduced from over 60% to approximately 55% also on a log-scale. The combined DCAP specific sources of uncertainty still provide relatively smaller contributions than the traditional sources of uncertainty.

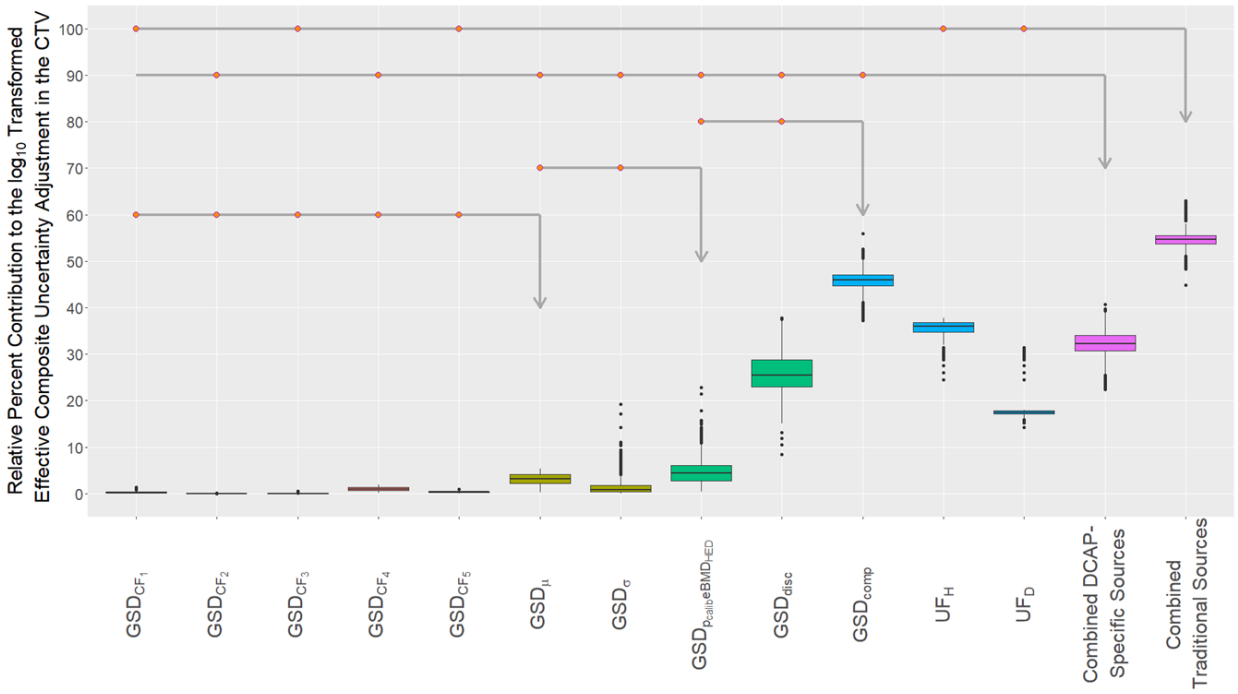


Figure 8-4. Boxplots of relative contributions of uncertainty components considered in the DCAP process to the effective composite uncertainty adjustment in the CTV with the alternative UF_D approach. The analysis was performed with the 193 chemicals used in the calibration process. The box represents the inter-quartile range between the 25th and 75th percentiles, while the horizontal line inside the box denotes the median. The whiskers represent the largest (or smallest) observation that is within 1.5 times the interquartile range above Q3 (or below Q1). Observations that fall outside the whiskers are shown individually as dots. Colors of the boxplots are grouped by their tiers of uncertainty adjustment application. The orange dots represent the uncertainty components that constitute the higher-tier uncertainty components indicated by the grey arrow.

8.7.4. COMPARISON OF CTV VALUES WITH REFERENCE DOSES FROM AUTHORITATIVE SOURCES USING THE ALTERNATIVE DATABASE UNCERTAINTY FACTOR

To compare the relative level of human health protection afforded by the DCAP using the alternative UF_D approach, **Figure 8-5** depicts a scatterplot of chronic RfD values from 56 IRIS and 33 PPRTV assessments compared to the corresponding DCAP-derived CTVs for the same chemicals. Based on the cumulative distribution plot, 64% of CTVs fall within an order of magnitude of the RfD values, and nearly 100% of the CTVs fall within two orders of magnitude (**Fig. 8-6**). When compared to all RfD values, 73% of CTV values are lower when compared to the corresponding RfD (*i.e.,* more conservative from a human health standpoint). When comparing separately with IRIS and PPRTVs, 82% of CTV values are lower than IRIS RfDs and 58% are lower than RfD values from PPRTVs. On the arithmetic scale, the median absolute ratio ± MAD between the RfD and CTV values is 4.4 $\pm$ 3.0.

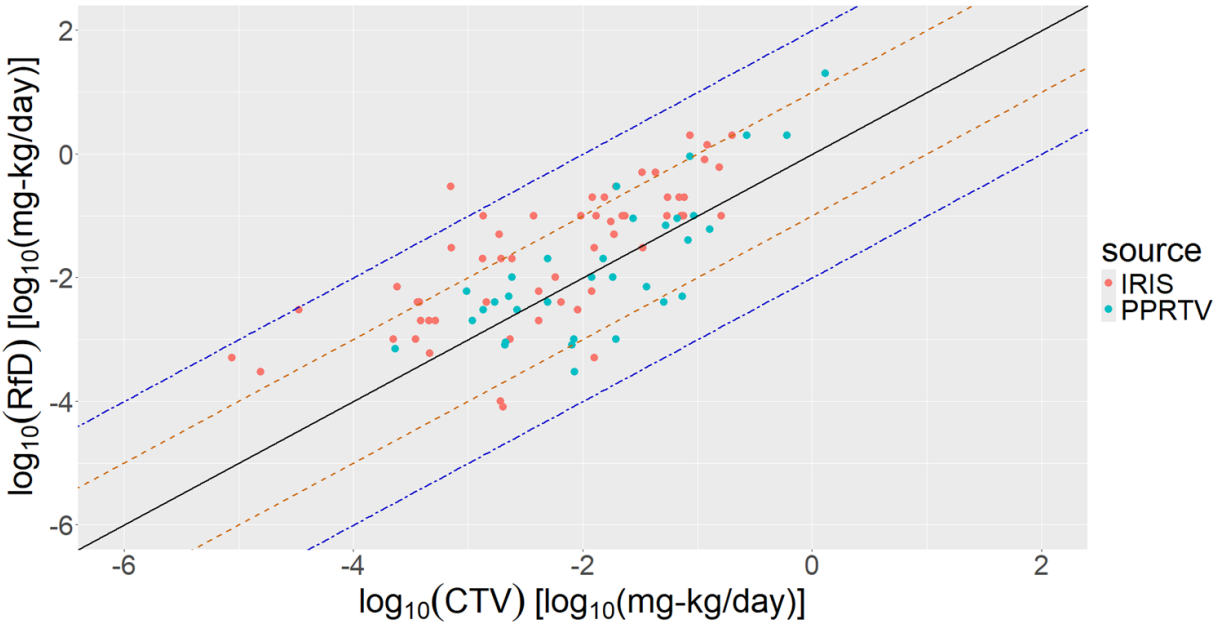


Figure 8-5. A comparison of CTV using the alternative UF_D approach and RfD values for 89 chemicals from IRIS (red) and PPRTV (blue). The black solid line represents CTV = RfD, while the orange and blue dotted lines represent $\pm\mathbf{1}$ and $\pm\mathbf{2}$ $\mathbf{log_{10}}$ difference, respectively.

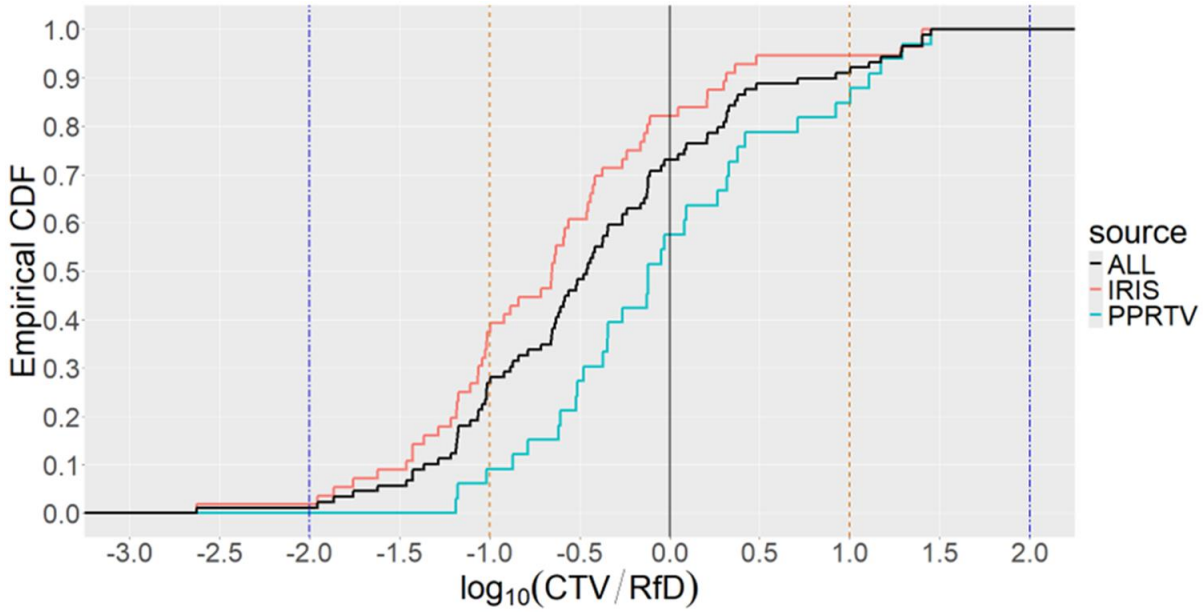


Figure 8-6. A cumulative distribution function (CDF) plot of the CTV-to-RfD ratio with the alternative UF_D approach for the 89 chemicals from IRIS (red) and PPRTV (blue) assessments. The black vertical solid line represents CTV = RfD, while the orange and blue dotted lines represent $\pm\mathbf{1}$ and $\pm\mathbf{2}$ $\mathbf{log_{10}}$ differences, respectively.