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EPA Database-Calibrated Assessment Product (DCAP) for Benzyltrimethylammonium chloride



Center for Computational Toxicology and Exposure (CCTE) Office of Research and Development U.S. Environmental Protection Agency

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Contents

DI	ISCLAIMER	2
AI	BBREVIATIONS	3
1	BACKGROUND	4
2	ASSESSMENT REVIEW	5
3	VERSION HISTORY	6
4	CHEMICAL IDENTITY AND PHYSICAL PROPERTIES	7
5	DATA SOURCES AND TOXICITY STUDIES	8
	5.1 DATA SOURCES	8
	5.2 TOXICITY STUDY RECORDS	8
6	STUDY CHARACTERISTICS	9
7	DOSE RESPONSE SUMMARY VALUE CHARACTERISTICS	10
8	CALCULATION OF THE CALIBRATED POINT OF DEPARTURE	12
	8.1 UNCERTAINTY IN eBMD _{HED} DISTRIBUTION	12
	8.2 UNCERTAINTY IN CALIBRATION PROCESS	13
9		
	DERIVATION OF THE CALIBRATED TOXICITY VALUE	14
	9.1 CALIBRATED POINT OF DEPARTURE	14 14
	9.1 CALIBRATED POINT OF DEPARTURE 9.2 CALIBRATED TOXICITY VALUE (CTV)	14 14 14
RI	9.1 CALIBRATED POINT OF DEPARTURE	14 14 14 15
RI	9.1 CALIBRATED POINT OF DEPARTURE 9.2 CALIBRATED TOXICITY VALUE (CTV) EFERENCES PPENDIX I	14 14 14 15 16
RI AI	9.1 CALIBRATED POINT OF DEPARTURE 9.2 CALIBRATED TOXICITY VALUE (CTV) 9.2 CALIBRATED TOXICITY VALUE (CTV)	14 14 15 16 17

DISCLAIMER

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ABBREVIATIONS

Abbreviations	Descriptions
BMD	Benchmark Dose
BMDL	Benchmark Dose Lower Confidence Limit
CASRN	Chemical Abstracts Service Registry Number
CCTE	Center for Computational Toxicology and Exposure
cPOD	Calibrated Point-of-Departure
CTV	Calibrated Toxicity Value
DCAP	Database-Calibrated Assessment Product
DRSV	Dose Response Summary Value
DSSTox	Distributed Structure-Searchable Toxicity Database
DTXSID	DSSTox Substance Identifier
eBMD	Estimated Benchmark Dose
eBMD _{HED}	Estimated Benchmark Dose, Human Equivalent Dose
ECUA	Effective Composite Uncertainty Adjustment
ECHA	European Chemicals Agency
EFSA	European Food Safety Agency
EPA	U.S. Environmental Protection Agency
GSD	Geometric Standard Deviation
HED	Human Equivalent Dose
IPCS	International Programme on Chemical Safety
IUPAC	International Union of Pure and Applied Chemistry
LEL	Lowest Effect Level
LOAEL	Lowest Observed Adverse Effect Level
LOEL	Lowest Observed Effect Level
NEL	No Effect Level
NN Histo	Non-Neoplastic Histopathology
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
ORD	Office of Research and Development
POD	Point of Departure
PPRIV	Provisional Peer-Reviewed Toxicity Values
QA	Quality Assurance
SMILES	Simplified Molecular-Input Line-Entry System
	Ioxicity Reference Database
IOXVAIDB	Ioxicity values Database
UF	Uncertainty Factor
	Animal-to-Human Interspecies variability Uncertainty Factor
	Database Uncertainty Factor
	Extrapolation of a LOAEL to NOAEL Upgortainty Easter
	Exitapolation of a LOAEL-10-INOAEL Uncertainty Factor
	Subcritonic-to-Ontonic Duration Extrapolation Uncertainty Factor World Health Organization
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1 BACKGROUND

Database-Calibrated Assessment Products (DCAP) are developed by the U.S. Environmental Protection Agency's (EPA) Office of Research and Development (ORD) to provide database calibrated toxicity values (CTV). The objective of this human health assessment is to provide a CTV with the level of confidence and caveats outlined in the Scientific Support and Standard Methods for the Development and Implementation of the EPA Database-Calibrated Assessment Product (DCAP) (EPA, 2024). 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 calibrated point-of-departure (cPOD) with uncertainties incorporated to reflect limitations of the data used. The cPOD is defined as the lower uncertainty limit of the value associated with the calibrated percentile in a distribution of chronic duration estimated human equivalent benchmark dose (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. While a CTV is expressly presented as a chronic value in the DCAP, it may also be applicable across other exposure durations of interest including short-term and subchronic. In certain human health assessments such as Provisional Peer Reviewed Toxicity Values (PPRTVs), EPA has adopted a chronic non-cancer reference value as a conservative estimate for a subchronic non-cancer reference value when data quality and/or lack of duration-relevant hazard and dose response data preclude direct derivation.

The DCAP method is intended to be applied to substances with existing, publicly accessible repeat dose toxicity studies, but lacking expert derived human health assessments from select authoritative sources. The DCAP is not intended to represent a comprehensive treatise on the chemical. The DCAP is not a risk assessment because it does not include an exposure assessment nor an overall risk characterization. Further, the human health assessment does not address the legal, political, social, economic, or technical considerations involved in risk management. The DCAP can be used by EPA, states, Tribes, and local communities, along with specific exposure and other relevant information, to determine if, and when, it is necessary to take action to address potential risk associated with human exposures to a chemical. Individual DCAPs may be updated to incorporate new data that might impact the CTV, or retired if an expert developed human health assessment is published from an authoritative source. A description of the underlying database and the methods associated with deriving the CTV are provided in *Scientific Support and Standard Methods for the Development and Implementation of the EPA Database-Calibrated Assessment Product (DCAP)* (EPA, 2024).

2 ASSESSMENT REVIEW

The methods for developing the DCAP outlined in this document have been internally reviewed by ORD scientists and management. The workflow has undergone a Technical Systems Audit for Quality Assurance, under the direction of the project Quality Assurance (QA) Manager, consistent with the QA process detailed in the DCAP methods. The methods are being externally peer reviewed by the EPA BOSC and subject to public comment (EPA, 2024).

This DCAP has followed the methods outlined in the *Scientific Support and Standard Methods for the De*velopment and Implementation of the EPA Database-Calibrated Assessment Product (DCAP) (EPA, 2024). Due to the extensive review of the standardized methods, this individual DCAP will not receive independent peer review.

3 VERSION HISTORY

DCAP are developed using *in vivo* toxicology data from multiple selected sources included within the ToxVal Database (ToxVaIDB). ToxVaIDB may be updated to include newly available data. In addition, the calibration of the optimal percentile that defines selection of the cPOD may also be update periodically to ensure that the calibration step is using the most up-to-date available information. For these reasons, version identifiers for the underlying dataset, the calibration procedure that informed the development of the current report, and the version of the DCAP assessment are provided in Table 1.

Table 1: Database and documentation version numbers underlying the DCAP

Item	Version Number	Date of Release (Month, Year)
ToxValDB	Version 9.6.0	December, 2024
DCAP Calibration Procedure	Version calib.1.2024	December, 2024
DCAP Assessment for DTXSID8024600	Version dcap.1.2024	December, 2024

4 CHEMICAL IDENTITY AND PHYSICAL PROPERTIES

Property	Value	Туре	
	H ₃ C H ₃ C H ₃ C		
Structure			
Name	Benzyltrimethylammonium chloride		
DTXSID	DTXSID8024600		
CASRN	56-93-9		
IUPAC name	N,N,N-Trimethyl(phenyl)methanaminium chloride		
Synonyms	-		
Molecular Weight	$C_{10}H_{16}ClN$		
SMILES	[CI-].C[N+](C)(C)CC1=CC=CC=C1		
Molecular weight	195 7		
(g/mol)	100.7		
Density	NA	-	
Boiling point (°C)	102.04		
(at 0.01 mm Hg)	195.04		
Melting point (°C)	238	Experimental	
LogP: octanol-water	-2.17	Experimental	
Henry's law constant	3.77e-02	OPERA Predicted	
Water solubility (mg/L)	8.54e-05	OPERA Predicted	
Vapor pressure (mm Hg)	9.06e-01	OPERA Predicted	

Table 2: Chemical identity and physicochemical properties of Benzyltrimethylammonium chloride.

5 DATA SOURCES AND TOXICITY STUDIES

5.1 DATA SOURCES

The DCAP was developed using the Toxicity Values database (ToxValDB)¹ Version 9.6.0.

5.2 TOXICITY STUDY RECORDS

Determination of eligible dose-response summary values (DRSVs) and their corresponding consolidated study groups were defined according to the filtering logic and selection hierarchies outlined within *Scientific Support and Standard Methods for the Development and Implementation of the EPA Database-Calibrated Assessment Product (DCAP)* (EPA, 2024). A total of 14 consolidated study groups were identified across eligible *in vivo* oral toxicity studies for Benzyltrimethylammonium chloride. A list of DCAP records for the consolidated groups is included in Appendix I.

¹The current, as well as prior, versions of EPA's ToxVaIDB is available at: https://www.epa.gov/comptox-tools/downloadable-computational-toxicology-data

6 STUDY CHARACTERISTICS

Across the 14 consolidated study groups, study characteristics are provided in the pie charts below (Figure 1).



Figure 1: Consolidated study group characteristics reported for Benzyltrimethylammonium chloride including (A) data sources; (B) standardized study types; (C) study durations; and (D) study species.

7 DOSE RESPONSE SUMMARY VALUE CHARACTERISTICS

Across the 14 consolidated study groups, the characteristics of the reported dose-response summary values (DRSVs) are provided in the pie charts below (Figure 2).



A. Standardized DRSV types

B. Standardized toxicological effect categories



Figure 2: DRSV characteristics reported for Benzyltrimethylammonium chloride including (A) standardized DRSV types; and (B) standardized toxicological effect categories. All NOAEL/NEL values are assigned a standardized toxicological effect category of 'none' since, by definition, no adverse effects are observed at the dose specified.

Following the *Scientific Support and Standard Methods for the Development and Implementation of the EPA Database-Calibrated Assessment Product (DCAP)* (EPA, 2024), the consolidated study groups were assigned a dose response model based on the standardized study type and standardized toxicological effect category. The source DRSVs were converted to eBMD_{HED} using WHO/IPCS guidance (2018). The resulting eBMD_{HED} values and reported DRSVs were distributed according to the box and whiskers plots provided below (Figure 3). The median, minimum, and maximum eBMD_{HED} values were 7, 1, and 65 mg/kg-day, respectively.



Figure 3: Box and whisker plots of the reported DRSVs (red) and chronic eBMD_{HED} values (blue) for Benzyltrimethylammonium chloride. 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.

8 CALCULATION OF THE CALIBRATED POINT OF DEPARTURE

The distribution of chronic $eBMD_{HED}$ values is fit to a lognormal distribution. The 18th percentile of the fitted distribution is most frequently associated with the POD for expert selected critical effects in human health assessments from select authoritative sources (EPA, 2024). For Benzyltrimethylammonium chloride, the 18th percentile of the $eBMD_{HED}$ distribution ($p_{calib}eBMD_{HED}$) is 2.6 mg/kg-day (0.42 log₁₀ mg/kg-day) (Figure 4).



Figure 4: Cumulative distribution of eBMD_{HED} values for Benzyltrimethylammonium chloride. The 18th percentile in the distribution (p_{calib}eBMD_{HED}) is highlighted with the red line.

8.1 UNCERTAINTY IN eBMD_{HED} DISTRIBUTION

The uncertainty in the estimation of $p_{calib}eBMD_{HED}$ flows from both the uncertainty in the conversion of the DRSVs to chronic $eBMD_{HED}$ values and the uncertainty in the inter-study variability. The geometric standard deviation² (GSD) associated with the estimation of μ (GSD $_{\mu}$) incorporates uncertainty from three traditional sources typically covered by uncertainty factors (UF) including 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), as well as other uncertainties that are unique to DCAP. The GSD_{σ} incorporates uncertainty in the estimation of the inter-study variability. For more information on how these uncertainties are included, please refer to the *Scientific Support and Standard Methods for the Development and Implementation of the EPA Database-Calibrated*

²GSDs are unitless factors that can be used to derive the lower and upper confidence bounds on a geometric mean by dividing and multiplying the geometric mean by the GSD, respectively. For the DCAP, GSDs are used in log₁₀-form rather than natural log.

Assessment Product (DCAP) (EPA, 2024) report. The uncertainties GSD_{μ} and GSD_{σ} are combined to provide an estimate of the total uncertainty in $p_{calib}eBMD_{HED}$. (Eq. 1).

$$GSD_{p_{calib} eBMD_{HED}}^{2} = 10^{\sqrt{(\log_{10}(GSD_{\mu}^{2}))^{2} + (\log_{10}(GSD_{\sigma}^{2}))^{2}}}$$
(1)

8.2 UNCERTAINTY IN CALIBRATION PROCESS

In addition to the uncertainty in $p_{calib}eBMD_{HED}$, the error associated with the calibration to the POD associated with critical effects from expert derived human health assessments was calculated as a GSD discordance (GSD_{disc}) of 5.02 (EPA, 2024). GSD_{comp} denotes the compounded GSD that combines the uncertainties associated with the eBMD_{HED} distribution and calibration process using Eq. 2.

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

Using the estimate of the total uncertainty, the lower 95th confidence bound on the $p_{calib}eBMD_{HED}$ was calculated as the cPOD (Eq. 3).

$$cPOD = \left(\frac{p_{calib}eBMD_{HED}}{GSD_{comp}^{z_{0.95}}}\right)$$
(3)

where $z_{0.95}$ denotes the z-score associated with 95th percentile of the standard normal distribution.

Table 3: Summary of estimates of the uncertainties for $p_{calib} eBMD_{HED}$ and the calibration process used to calculate the cPOD for Benzyltrimethylammonium chloride

GSD_{μ}^{*}	GSD_σ	$\mathrm{GSD}_{p_{\mathrm{calib}} \ \mathrm{eBMD}_{\mathrm{HED}}}$	$\mathrm{GSD}_{\mathrm{disc}}$	$\mathrm{GSD}_{\mathrm{comp}}$
1.7	1.2	1.8	5	5.6

^{*} The GSD_{μ} includes three traditional sources of uncertainty normally associated with UF_{S} , UF_{L} and UF_{A} .

9 DERIVATION OF THE CALIBRATED TOXICITY VALUE

9.1 CALIBRATED POINT OF DEPARTURE

The lower uncertainty limit on the $p_{calib}eBMD_{HED}$ of 0.16 mg/kg-day was determined to be the cPOD for Benzyltrimethylammonium chloride. 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 (EPA, 2024). 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.

9.2 CALIBRATED TOXICITY VALUE (CTV)

The application of UF follows the procedure described in the *Scientific Support and Standard Methods for the Development and Implementation of the EPA Database-Calibrated Assessment Product (DCAP)* (EPA, 2024). Uncertainty associated with animal-to-human extrapolation (UF_A), extrapolation from a LOAEL to a NOAEL when a NOAEL is not available (UF_L), and extrapolation from shorter-duration studies to chronic duration (UF_S) are all integrated into the calculation of a cPOD. Additional quantitative application of a UF for intraspecies variability (UF_H) and the toxicity database (UF_D) are considered in the derivation of the CTV, as these specific UF are not accounted for in the calculation of the cPOD (Table 4). DCAP universally applies an UF_H of 10 for all chemicals to account for interindividual variability in the susceptibility of the human population due to both intrinsic and extrinsic factors that can influence the response to exposure dose. A UF_D of 10 is applied in the derivation of the CTV to account for a lack of qualitative confidence characterization of the hazard data and potential data gaps in the underlying toxicity database.

Table 4: Uncertainty factors used in the calculation of the CTV for Benzyltrimethylammonium chloride

UF	Value	Description
UFA	*	The UF_{A} is incorporated into the calculation of the cPOD.
UFs	*	The UF_S is incorporated into the calculation of the cPOD.
UFL	*	The UF_L is incorporated into the calculation of the cPOD.
UF_H	10	A ${\rm UF}_{\rm H}$ is applied to account for interindividual variability in the susceptibility of the human population.
UF_D	10	A UF_D is applied to account for lack of qualitative confidence characterization of the hazard data, and potential data gaps in the underlying toxicity database.

 * The asterisk associated with $\rm UF_A, \, UF_S,$ and $\rm UF_L$ signifies that these specific uncertainties were quantitatively accounted for in the calculation of the cPOD. The remaining factors of 10 are associated with the $\rm UF_H$ and $\rm UF_D$, respectively.

Using the cPOD of 0.16 mg/kg-day, the CTV was calculated based on Equation 4:

$$CTV = \frac{cPOD}{UF_{A}^{*} \times UF_{S}^{*} \times UF_{L}^{*} \times UF_{H} \times UF_{D}} = \frac{0.16 \text{ mg/kg-day}}{10 \times 10} = 0.0016 \text{ mg/kg-day}$$
(4)

The CTV for Benzyltrimethylammonium chloride is 0.0016 mg/kg-day and is an estimate of the 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 additional uncertainty factors applied to reflect limitations of the data used.

REFERENCES

EPA. 2024. Scientific Support and Standard Methods for the Development and Implementation of the EPA Database Calibrated Assessment Product (DCAP). DRAFT. Research Triangle Park, NC:U.S. Environmental Protection Agency.

WHO. 2018. Guidance document on evaluating and expressing uncertainty in hazard characterization. Harmonization Project Document 11 – 2nd edition. Geneva, Switzerland:World Health Organization, International Programme on Chemical Safety.

APPENDIX I

The following table includes the source documents from which each dose response summary value (DRSV) for the chemical under assessment was derived. Selection of DRSVs for use in the assessment from the underlying source documents was accomplished using the data filtering and selection hierarchies as described in the *Scientific Support and Standard Methods for the Development and Implementation of the EPA Database-Calibrated Assessment Product (DCAP)* (EPA, 2024).

Standardized DRSV Type	DRSV (mg/kg-day)	Standardized Study Duration	Study Species	Standardized Toxicological Effect Category	Information Source	Source Record Location
NOAEL	20.0	reproductive developmental	Rat	none	ECHA IUCLID	url
NOAEL	20.0	reproductive developmental	Rat	none	ECHA IUCLID	url
NOAEL	100.0	reproductive developmental	Mouse	none	ECHA IUCLID	url
NOAEL	100.0	reproductive developmental	Rat	none	ECHA IUCLID	url
LOAEL	50.0	subchronic	Mouse	other	ECHA IUCLID	url
NOAEL	25.0	subchronic	Rat	none	ECHA IUCLID	url
LOAEL	63.0	short-term	Rat	other	ECHA IUCLID	url
LOAEL	125.0	short-term	Mouse	other	ECHA IUCLID	url
LOAEL	250.0	short-term	Mouse	other	ECHA IUCLID	url
LOAEL	12.5	subchronic	Rat	multiple	NITE HESS	url
NOAEL	25.0	subchronic	Rat	none	EPA HPVIS	url
NOAEL	25.0	subchronic	Mouse	none	EPA HPVIS	url
NOAEL	60.0	short-term	Rat	none	EPA HPVIS	url
NOAEL	30.0	short-term	Rat	none	EPA HPVIS	url

Table 5: Data source information of DRSVs for Benzyltrimethylammonium chloride extracted from ToxValDB.

Records in Table 5 may appear as duplicates, however the records will differ based on study group characteristics not shown in the table. These differences include, but are not limited to, life stage or sex represented by the study group or independent studies with similar characteristics resulting in the same DRSV.

APPENDIX II

RELATIVE CONTRIBUTIONS TO THE EFFECTIVE COMPOSITE UNCERTAINTY ADJUSTMENT

The DCAP process incorporates adjustments to account for uncertainties and interindividual human variability. These adjustments apply to the derivation of the cPOD and the derivation of the CTV. The effective composite uncertainty adjustment (ECUA) in the CTV, defined as the ratio of $p_{calib}eBMD_{HED}$ and the CTV, can be partitioned into three components: GSD_{comp} , UF_H, and UF_D, as

$$ECUA = \frac{p_{calib}eBMD_{HED}}{CTV} = \frac{p_{calib}eBMD_{HED}}{GSD_{comp}^{z_{0.95}} \times UF_{H} \times UF_{D}}$$
(5)

The ECUA for Benzyltrimethylammonium chloride is 1679.

Their relative contribution to the overall uncertainty adjustment can be described using their respective log-reductions. For example, $UF_H = 10$ and $UF_D = 10$ indicate that they each reduce the CTV by $log_{10}(10) = 1$ order of magnitude, and therefore their relative contribution can be calculated as

$$\frac{\log_{10}(\cdot)}{\log_{10}(\text{GSD}_{\text{comp}}^{z_{0.95}} \times \text{UF}_{\text{H}} \times \text{UF}_{\text{D}})}$$
(6)

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

Figure 5 provides the relative percent contribution to the ECUA in the CTV derivation for Benzyltrimethylammonium chloride. These percentages may not add up to 100% due to the compounding of uncertainties in the DCAP process.



Figure 5: Relative percent contribution to the effective composite uncertainty adjustment in the CTV for Benzyltrimethylammonium chloride. Orange bars are the uncertainties surrounding the conversion of the DRSVs to $eBMD_{HED} (GSD_{\mu})$ and the inter-study variability (GSD_{σ}) . The first green bar $(p_{calib} eBMD_{HED})$ is the combined uncertainty from GSD_{μ} and GSD_{σ} . The second green bar (GSD_{disc}) is the uncertainty from the calibration process. The first blue bar (GSD_{comp}) is the combined uncertainty from the two green bars. The blue bars representing UF_{H} and UF_{D} are the uncertainty factors used to account for variation in the susceptibility within the human population and lack of a complete database, respectively.