BBP Butyl Benzyl Phthalate Consortium

Dibutyl Phthalate Consortium
Managed by B&C® Consortia Management, L.L.C.

Di-ethylhexyl Phthalate Consortium
Managed by B&C® Consortia Management, L.L.C.

DIBP Di-isobutyl Phthalate Consortium
Managed by B&C® Consortia Management, L.L.C.

July 25, 2025

Via Docket
Via E-Mail

Alaa Kamel, Ph.D.
Mission Support Division
Office of Program Support
Office of Chemical Safety and Pollution Prevention
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460-0001

Re: Comments on Draft Cumulative Risk Analysis of Phthalates (EPA-HQ-OPPT-2024-0551)

Dear Dr. Kamel:

B&C® Consortia Management, L.L.C. (BCCM), on behalf of the members of the Butyl Benzyl Phthalate Consortium[1] (BBP Consortium), the Dibutyl Phthalate Consortium[2] (DBP Consortium), the Di-ethylhexyl Phthalate Consortium[3] (DEHP Consortium), and the Di-isobutyl Phthalate Consortium[4] (DIBP Consortium), is pleased to provide for Scientific Advisory Committee

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[1] The BBP Consortium membership includes Henkel Corporation; Polymer Additives, Inc., DBA Valtris Specialty Chemicals; Tremco Incorporated; and The Sherwin-Williams Company.

[2] The DBP Consortium membership includes Henkel Corporation, Huntsman International, and The Sherwin-Williams Company.

[3] The DEHP Consortium membership includes Eastman Chemical Company, Henkel Corporation, and R.E. Carroll, Inc.

[4] The DIBP Consortium membership includes LyondellBasell and W.R. Grace & Co.-Conn.

on Chemicals (SACC) consideration comments on the cross-phthalate technical support documents (TSD) for the draft revised cumulative risk assessment (CRA) under the U.S. Environmental Protection Agency's (EPA) Toxic Substances Control Act (TSCA).

The BBP Consortium, DBP Consortium, DEHP Consortium, and DIBP Consortium (collectively, the consortia) consist of manufacturers, importers, and users of butyl benzyl phthalate (BBP; Chemical Abstracts Service Registry Number® (CAS RN®) 85-68-7), dibutyl phthalate (DBP; CAS RN 84-74-2), di-ethylhexyl phthalate (DEHP; CAS RN 117-81-7), and di-isobutyl phthalate (DIBP; CAS RN 84-69-5), respectively.

The consortia commend EPA for advancing the CRA for phthalates and commissioning the SACC to conduct the peer review. The CRA is a novel and important assessment that will significantly influence how cumulative assessments will be undertaken for years to come. The consortia stress that it is critical the CRA rely upon the best available science as required by TSCA.

We have identified several areas of concern, including EPA's approach to benchmark dose (BMD) modeling, selection of points of departure (POD), and derivation of relative potency factors (RPF), that we urge the SACC to review and on which to provide comment for EPA's consideration when it prepares the CRA in final. The following sections provide additional details regarding our concerns.

I. BMD Values

EPA did not follow its own Benchmark Dose Technical Guidance document while estimating the risk of the five phthalates in the CRA. EPA's BMD Guidance (p. 21) recommends a benchmark response (BMR) of 5% extra risk (BMR_5) for quantal endpoints in developmental toxicology studies that are adequately powered to detect such levels of change. The BMD Guidance does not, however, recommend a BMR of 5% relative deviation for continuous endpoints, such as fetal testicular testosterone (FTT).

As discussed in EPA's BMD Guidance, developmental toxicity studies with nested study designs provide increased statistical power compared to regular toxicity studies due to the increase in sample size (*i.e.*, use of pups as the observational subject), and as such, a BMR_5 is supported when modeling only quantal data obtained from these studies. EPA's use of a BMR of 10% deviation relative to control mean was not sufficiently justified or explained for its use in a continuous data set. The use of a BMR of 40% deviation relative to control (BMR_{40}) is no longer supported given data from Howdeshell *et al*., 2015. Howdeshell found a 25% reduction in fetal testosterone was associated with 17% incidence of reproductive tract malformations (RTM) in F1 males.

II. In Assessing Occupational Exposure Values, EPA's Approach Is Inconsistent and Lacks Transparency in Selecting PODs

EPA's use of FTT production for its BMD modeling is supported as a suitable choice in selecting PODs. FTT is an early event in the adverse outcome pathway (AOP) and the molecular initiating event is still considered unknown in preference to the use of gene expression levels, given the inherent variability between messenger ribonucleic acid (mRNA) expression with enzyme levels.

Although EPA is assessing phthalates cumulatively, it did not consistently select PODs, as shown below in Table 1. EPA is required under TSCA to apply a consistent and transparent approach to determine regulatory limits of individual phthalates.

EPA did not provide a justification for using the no observed adverse effect level (NOAEL) in deriving the occupational exposure value (OEV) instead of the benchmark dose lower confidence limit (BMDL$_5$) for dicyclohexyl phthalate (DCHP; CAS RN 84-61-7). EPA also did not include a discussion of the modeling issues that arose or an explanation as to why the BMDL$_5$ was not selected. Finally, EPA did not discuss the impacts of data limitations on the results from the alternate NOAEL approach. EPA's failure to provide sufficient justification or explanation for how it derived the OEVs does not meet the legal imperative under TSCA to use the best available science.

Table 1. EPA-Derived PODs and OEVs for Phthalates

Chemical	POD Selected by EPA (mg/kg-bw/day)		Metafor Version 2.0.0			Metafor Version 4.6.0			NOAEL[*] (mg/kg-bw/day)	Lowest LOAEL (mg/kg-bw/day)
			BMDL 5	BMDL 10	BMDL 40	BMDL 5	BMDL 10	BMDL 40		
DCHP	NOAEL	**10**	6.5	13	69	6	12	63	**10** to 17	20 to 33
BBP	NOAEL	**50**	17	36	179	-	-	150	33/**50**[**]	100
DBP	BMDL$_5$	**9**	11	23	119	**9**	20	101	10	1 to 10
DEHP	NOAEL	**4.8**	12	26	134	11	24	122	**4.8**	10 to 17
DINP	BMDL$_5$ NOAEL $_{chronic}$	**49** **15**	52	108	584	47	97	539	50$_{acute}$ **15**$_{\mathbf{chronic}}$	600
DIBP	BMDL$_5$	**24**	23	47	239	-	-	136	100	125 to 200

$BMDL_x$ is the BMDL lower confidence limit for the BMR_x.
- Signifies that modeling was not able to derive these values.
Bolded text signifies the value used by EPA to derive OEVs.
[*] NOAELs are based on fetal testosterone production.
[**] NOAEL of 50 mg/kg-bw/day from a multi-generational study based on decreased anogenital distance (AGD) (Tyl *et al.*, 2004). We propose the POD and NOAEL used for deriving the OEV as 33 mg/kg-bw/day for fetal testosterone production (Gray *et al.*, 2021 and Furr *et al.*, 2014).

As shown in Table 1, it is not always clear which value EPA used in establishing the PODs. For DCHP, BBP, DBP, DIBP, and DEHP, the value that EPA selected matches the value of a corresponding metric (BMDL$_5$ or NOAEL). For diisononyl phthalate (DINP; CAS RNs 28553-12-0 and 68515-48-0), EPA specified a BMDL$_5$ of 49 for the POD, which is a mismatch with the Metafor

Version 4.6.0 value of 47. For DIBP, it is not transparent that the value was derived from the $BMDL_5$ of an individual study (*i.e.*, Gray *et al.*, 2021) and not the entire available modeling data set for fetal testosterone production, which is shown here as undefined (-). The omission of Furr *et al.*, 2014 in BMD modeling used to derive the OEV for DIBP was not discussed in regard to its frequent use in BMD modeling for other phthalates.

EPA did not utilize model averaging approaches but rather selected a best fitting model based on the lowest Akaike information criterion (AIC). This is not consistent with BMD modeling best practices as there is no guarantee that the best fitting model fits the true dose-response relationship. This approach, selecting a single model from a group of fitted models, has been shown to lead to model uncertainty (Shao and Gift, 2014; Piegorsch *et al*., 2013; Wheeler and Bailer, 2007). Model averaging has emerged as the preferred method to address model uncertainty concerns by including the results of several models (appropriately averaged) when estimating BMDL values. For these reasons, the consortia urge EPA to utilize model averaging approaches whenever possible. While ToxicR and the Bayesian Benchmark Dose (BBMD) System are both capable of utilizing model averaging approaches to model continuous data, Metafor does not appear to have this capability. The use of the new version of Metafor (4.6.0 versus 2.0.0) over ToxicR or BBMD was not justified.

III. Proposed Hierarchy Selection for Deriving the POD

EPA should select a common endpoint for which it has data for all the subject substances, in this case, FTT production, rather than selecting different endpoints for different substances. Instead of EPA's inconsistent use of the $BMDL_5$ from Metafor Version 4.6.0 and the use of the NOAEL for different endpoints when deriving OEVs, the consortia propose the creation of a hierarchy for determining the POD that represents the best available science.

We urge EPA to conduct modeling again according to EPA's BMD Guidance using a BMR equal to one control standard deviation (SD). Modeling should also be conducted using ToxicR and/or BBMD using a model averaging approach to align with the best available science. Then a hierarchy for the selection of the POD should be applied to allow for consistency between phthalates. If the value for any model output is outside of an acceptable range (*i.e.,* exceeding the lowest observed adverse effect level (LOAEL)) or is not supported by the available data, EPA should proceed to the next level of the hierarchy.

1. BBMD/ToxicR Modeling Average $BMDL_{1SD}$
2. NOAEL
3. LOAEL

IV. Example Application of Hierarchy in Derivation of PODs

The values in Table 2 are intended to capture the proposed hierarchy for POD selection and are provided as examples for the selection of PODs that result in consistency among the phthalates while also providing transparency. The consortia urge EPA to ensure that its BMD modeling approach uses the most appropriate data sets available for the common endpoint, fetal testosterone production.

A. DCHP

Using the proposed hierarchy, the consortia conducted BMD modeling using a change in the mean equal to one control SD from the control mean. This analysis was conducted using the calculated combined mean and SD based on the three test groups in Gray *et al.*, 2021 and Furr *et al.*, 2014, to align with EPA's BMD modeling. Modeling was then conducted using BBMD using a model averaging approach to align with the best available science.

Table 2. BBMD Modeling Averaging Results for DCHP

Substance and Data Set	BMDL values calculated from Modeling Averaging Curve (mg/kg-bw/day)				NOAEL (mg/kg-bw/day)	Lowest LOAEL (mg/kg-bw/day)
	$BMDL_{1SD}$	$BMDL_5$	$BMDL_{10}$	$BMDL_{40}$		
DCHP Combined Data Set	19.58	3.47	7.33	44.82	10* to 17**	20 to 33***

* Li *et al.*, 2016
** Hoshino *et al.*, 2005
*** Ahbab *et al.*, 2017; Ahbab and Barlas, 2015; Furr *et al.*, 2014; Ahbab and Barlas, 2013

The use of $BMDL_{1SD}$ aligns with the best available science as it allows for the use of a biologically relevant and consistent endpoint (*i.e.,* FTT) for comparison with other phthalates. This value is supported by EPA's BMD Guidance, as suggested above, and aligns with currently available data set NOAELs/LOAELs. Using the $BMDL_{1SD}$, we propose the following OEVs for DCHP.

Table 3. DCHP OEVs

Substance	Basis for POD; critical effect	Adjusted POD	OEVs
DCHP	$BMDL_{1SD}$ of 19.58 mg/kg-bw/day	HED*: 4.6 mg/kg-bw/day HEC**: 25.1 mg/m^3	EV_{acute} = 1.23 mg/m^3 $EV_{intermediate}$ = 1.68 mg/m^3 $EV_{chronic}$ = 1.80 mg/m^3

* HED: Human equivalent dose.
** HEC: Human equivalent concentration.

The proposed POD is supported by a NOAEL of 17 mg/kg-bw/day for signs of phthalate syndrome in Hoshino *et al.*, 2005 and four other studies reporting effects on the developing male reproductive system consistent with a disruption of androgen action and phthalate syndrome in rats at LOAELs ranging from 20 to 33 mg/kg-day (Ahbab *et al.*, 2017; Ahbab and Barlas, 2015; Furr *et al.*, 2014; Ahbab and Barlas, 2013) as indicated in EPA's draft risk evaluation on DCHP.

V. Updated PODs for Individual Phthalates

Table 4 contains the proposed PODs obtained with the use of BBMD using a model averaging approach to align with the best available science. The studies used in modeling align with key study and biological variables that are crucial for cross-study comparison. The metrics that must be matched across studies include: gestation day (GD) at time of tissue collection to control for fluctuations of testosterone during development, time of day of tissue collection to control for daily circadian rhythmicity of testosterone, and fetal testicular testosterone sampling methods to control the quantification method. When modeling did not align with the proposed hierarchy, the OEV was calculated using the NOAEL, as seen with BBP and DEHP. In these cases, BMD modeling was then conducted on individual studies or appropriately grouped studies to allow for alignment in deriving an RPF value, as seen with DEHP.

With DBP, the wide range of FTT levels in the control groups invites the question whether there is biological significance to the changes in FTT levels observed following DBP exposures or if the data used in BMD analysis are not adequately controlled (*e.g.*, by time of day to control for circadian cyclicity of testosterone or by sampling technique and analytical methodology). Due to this uncertainty, BMD modeling with BBMD was not achievable for DBP using best available science.

Table 4. Updated PODs for Individual Phthalates for OEV and RPF

Chemical	Updated POD for Individual Phthalate		NOAEL (mg/kg-bw/day)	Lowest LOAEL (mg/kg-bw/day)	POD for FTT and RPF		NOAEL (mg/kg-bw/day) for FTT	Lowest LOAEL (mg/kg-bw/day) for FTT
DCHP	$BMDL_{1SD}$	19.58	10 to 17	20 to 33	$BMDL_{1SD}$	19.58	-	33
BBP	$BMDL_{1SD}$	61.44	50	100	$BMDL_{1SD}$	61.44	33	100
DBP	NOAEL	10	10	1 to 10	NOAEL	10	10	33
DEHP	NOAEL	4.8	4.8	10 to 17	$BMDL_{1SD}$	17.96	10	50
DIBP	$BMDL_{1SD}$	113.4	100	125	$BMDL_{1SD}$	113.4	100	200

VI. Derivation of RPFs

The use of a BMR_{40} for decreased FTT to derive the RPFs for the different phthalates, while using DBP as the index chemical, does not represent the best available science. The use of BMR_{40} is also suspect given results for Howdeshell *et al.*, 2015, as defined above. The BMR_{40} values are ill-suitable to derive OEVs because all the BMR_{40} values exceed the lowest LOAEL. This incorrectly suggests DCHP is the most hazardous substance, when currently available data based on the NOAEL and EPA's POD selected for phthalate syndrome suggest that DEHP would be the lowest POD based on the current data set (*see* Section II). The consortia believe that EPA's inconsistent use of endpoints (AGD, RTM, and fetal testosterone) for deriving OEV or RPF values is not compliant with TSCA.

Table 5 shows the proposed updated RPF values based on a consistent endpoint under the same variables using the best available science. DBP was based on the NOAEL from Furr *et al.*, 2014 and aligned with the same variables used in the BMD modeling of the other phthalates (*e.g.*, GD and sampling methods). The NOAEL was used for DBP as it was the only phthalate where a $BMDL_{1SD}$ could not be derived due to the inherent variability within the data set.

Table 5. Proposed RPFs

Chemical	Proposed RPF			EPA's RPF		
	POD for RPF_{FTT}		RPF_{FTT}	$BMDL_{40}$ for FTT		RPF_{40}
DCHP	$BMDL_{1SD}$	19.58	0.51	$BMDL_{40}$	90	1.66
BBP	$BMDL_{1SD}$	61.44	0.16	$BMDL_{40}$	284	0.52
DBP	NOAEL	10	1.00	$BMDL_{40}$	149	1.00
DEHP	$BMDL_{1SD}$	17.96	0.56	$BMDL_{40}$	178	0.84
DIBP	$BMDL_{1SD}$	113.4	0.09	$BMDL_{40}$	279	0.53

VII. Conclusion

For all the reasons discussed above, the consortia commend EPA for the progress it has made in its risk evaluation for the CRA of phthalates, but urge EPA to address the deficiencies outlined above that do not meet TSCA requirements to use the best available science and adhere to EPA's own guidelines. EPA's generation of PODs lacks transparency and consistency. The consortia urge EPA to recalculate BMR based on a change in the mean equal to one control SD from the control mean and derive PODs and RPFs to use as a basis for its risk calculations and the derivation of OEVs. The creation of a validated method of detection must be in place prior to the identification of enforceable control measures and regulatory limitations.

The consortia appreciate the SACC's consideration of these comments. If the SACC has any questions, please contact me at jogden@bc-cm.com or 202-833-6581.

Sincerely,

Julianne M. Ogden
Consortia Manager

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