3 steps to Cumulative Phthalate Risk Assessment

1. **Determine intake** - back-calculate intake (µg/kg/day) from urinary metabolites (µg/L)

Table 3. Selected percentiles of estimated daily intake (µg/kg/day) for six phthalates examined from the 2007/2008 NHANES data set

	5%	10%	25%	50%	75%	90%	95%
DBP	0.12	0.18	0.29	0.54	0.98	1.65	2.43
DiBP	0.04	0.06	0.12	0.22	0.38	0.60	0.92
BBP	0.04	0.06	0.13	0.26	0.58	1.14	1.69
DEHP	0.56	0.72	1.14	2.09	4.28	10.12	20.38
DINP	0.29	0.39	0.61	1.11	2.34	5.28	9.36
DIDP	0.11	0.16	0.26	0.47	0.92	1.75	2.84

Abbreviations: BBP, butyl-benzyl phthalate; DBP, di-butyl phthalate; DEHP, bis(2-ethylhexyl) phthalate; DiBP, di-isobutyl phthalate; DIDP, di-isodecyl phthalate; DINP, di-isononyl phthalate; NHANES, National Health and Nutrition Examination Survey.
Values were calculated using sample data and Eq. (1)

Assessment of chemical coexposure patterns based upon phthalate biomonitoring data within the 2007/2008 National Health and Nutrition Examination Survey .J Expo Sci Environ Epidemiol. 2015,25(3):249-55.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4408491/

Daily Intake Estimates (ug/kg-day) for Women of Reproductive Age, median and 95th percentiles, NHANES 2005-2012; 2013-2014 (CHAP, 2017). https://www.cpsc.gov/chap

NHANES Data Set	BBP	DEHP	DINP	DBP	DIBP
Median					
NHANES 2005/2006	0.26	3.8	1.0	0.69	0.19
NHANES 2007/2008	0.29	4.1	1.5	0.79	0.29
NHANES 2009/2010	0.23	2.0	3.0	0.58	0.32
NHANES 2011/2012	0.19	1.7	5.0	0.33	0.26
95th Percentile					
NHANES 2005/2006	1.1	27.7	10.5	2.6	0.82*
NHANES 2007/2008	1.3	31.5	14.6	2.6	1.0
NHANES 2009/2010	1.0	10.3*	33.7	1.9*	0.98
NHANES 2011/2012	0.84	6.4*	51.7	1.3	0.94

*Variance estimates can be large at the 95th percentile. Marked estimates are not considered stable. Use caution when drawing conclusions using 95th percentile estimates.

2. Calculate Hazard Quotient (HQ): how does daily intake compare to reference concentration

$$HQ: \quad Daily\ Phthalate\ Intake/Phthalate\ RfC$$

Phthalate, source	EU: (EFSA, 2005a,b,c,d) Tolerable Daily Intake
DEHP	TDI = 50 µg/kg-day (Testis-related parameters: ↓ testicular weight, small or aplastic testes, seminiferous tubular atrophy, infertility) (EFSA, 2005c) NOAEL = 5 mg/kg-day (5000 µg/kg-day) Total UF = 100
DBP	TDI = 10 µg/kg-day (↓ Number of spermatocytes) (EFSA, 2005b) LOAEL = 2 mg/kg-day (2000 µg/kg-day) Total UF = 200
BBP	TDI = 500 µg/kg-day (↓ Anogenital distance) (EFSA, 2005d) NOAEL = 50 mg/kg-day (50,000 µg/kg-day) Total UF = 100
DiNP	TDI = 150 µg/kg-day (↑ Incidence of spongiosis hepatis, accompanied by ↑ serum levels of liver enzymes and absolute and relative liver and kidney weights in both sexes) (EFSA, 2005a) NOAEL = 15 mg/kg-day (15,000 µg/kg-day) Total UF = 100
DiBP	–

Generation of hazard indices for cumulative exposure to phthalates for use in cumulative risk assessment Reg Tox Pharmacol 69 (2014) 380–389

3. Calculate Hazard Index: Sum HQ for each phthalate = HQ_1 + HQ_2 + HQ_3 …

Hazard Quotients[*] calculated for each set of reference values.

| Phthalate	Population[*]	EU TDI	
		Median (25th–75th percentile)	95th percentile
BBzP	All ages ⩾6 yrs	0.0005 (0.0002–0.001)	0.003
	Ages 6–11 yrs	0.001 (0.0007–0.003)	0.007
	Women, ages 18–39 yrs	0.0006 (0.0003–0.001)	0.003
	Men, ages 18–39 yrs	0.0006 (0.0003–0.001)	0.002
DBP	All ages ⩾6 yrs	0.05 (0.03–0.09)	0.21
	Ages 6–11 yrs	0.09 (0.06–0.14)	0.35
	Women, ages 18–39 yrs	0.06 (0.04–0.10)	0.22
	Men, ages 18–39 yrs	0.05 (0.03–0.09)	0.16
DiBP	All ages ⩾6 yrs	–	–
	Ages 6–11 yrs	–	–
	Women, ages 18–39 yrs	–	–
	Men, ages 18–39 yrs	–	–
DEHP	All ages ⩾ 6 yrs	0.07 (0.04–0.15)	0.69
	Ages 6–11 yrs	0.12 (0.07–0.22)	0.81
	Women, ages 18–39 yrs	0.08 (0.05–0.18)	0.69
	Men, ages 18–39 yrs	0.08 (0.04–0.19)	0.94
DiNP	All ages ⩾6 yrs	0.01 (0.005–0.02)	0.08
	Ages 6–11 yrs	0.02 (0.01–0.03)	0.09
	Women, ages 18–39 yrs	0.01 (0.005–0.02)	0.09
	Men, ages 18–39 yrs	0.01 (0.005–0.02)	0.09
DEHP, Alternate value[†]	All ages ⩾6 yrs	1.18 (0.65–2.52)	11.50
	Ages 6–11 yrs	1.99 (1.23–3.53)	13.58
	Women, ages 18–39 yrs	1.41 (0.82–2.95)	11.48
	Men, ages 18–39 yrs	1.31 (0.73–3.10)	15.69

HAZARD INDEX: Women = 1.0   Men = 1.2

To add phthalates of different toxicity, scale HQ based on phthalate potency:

| phthalate | daily intake (µg/kg/day) [2001–2012, N = 2842] | | | daily intake (µg/kg/day) [2005–2012, N = 1723] | | | BMD (mg/kg/day) | RPF | mean contribution to Σandrogen-disruptor | |
	GM	95% CI		GM	95% CI				model 1[a]	model 2a[b]
di-*n*-butyl phthalate (DnBP)	0.60	0.57	0.63	0.54	0.51	0.57	30	1.000	0.29	0.18
diisobutyl phthalate (DiBP)	0.19	0.18	0.20	0.24	0.23	0.26	126	0.240	0.03	0.02
butyl benzyl phthalate (BBzP)	0.26	0.25	0.27	0.22	0.21	0.24	116	0.260	0.04	0.03
di(2-ethylhexyl) phthalate (DEHP)[c]	2.52	2.36	2.69	2.88	2.65	3.13	49	0.610	0.64	0.48
diethyl phthalate (DEP)	–	–	–	2.47	2.25	2.72	–	0.024	–	0.04
diisononyl phthalate (DiNP)	–	–	–	2.40	2.14	2.68	–	0.260	–	0.25

A Novel Method for Calculating Potency-Weighted Cumulative Phthalates Exposure with Implications for Identifying Racial/Ethnic Disparities among U.S. Reproductive-Aged Women in NHANES 2001-2012.
Environ Sci Technol. 2016 Oct 4;50(19):10616-10624. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5748889/

CUMULATIVE PHTHALATE EXPOSURE – how frequently do "phthalate groups" occur in humans?.

Frequency of Phthalate Mixtures in NHANES data
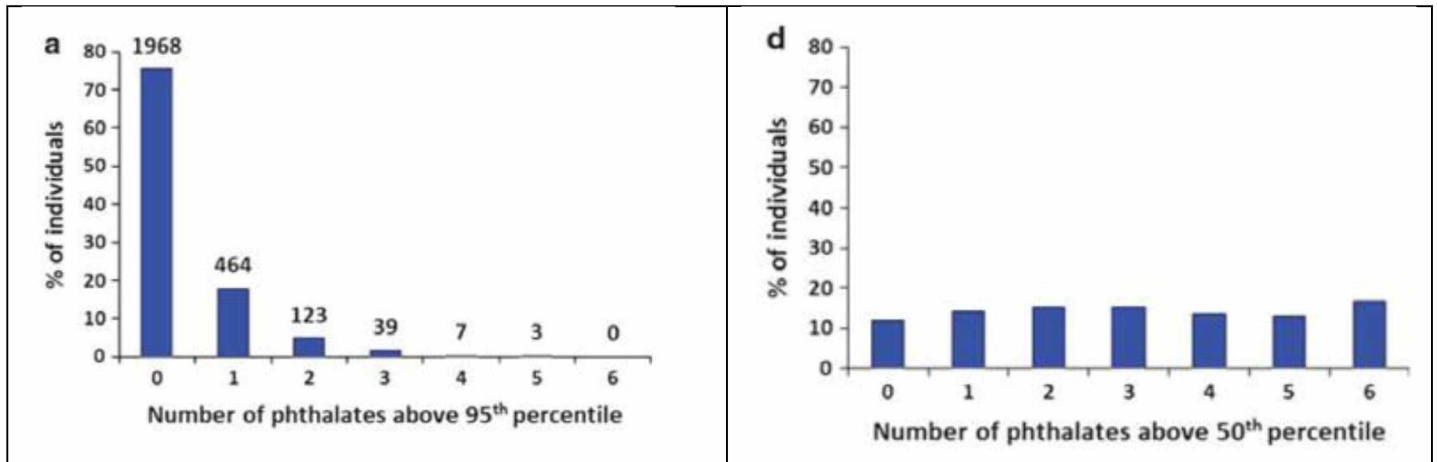
Percentage of individuals with number of phthalates above the 95th and 50th of NHANES intake.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4408491/

How often does HI ≥ 1.0 in NHANES data?
Frequency of phthalate pairs for 21 participants with HI > 1 (n=2663, NHANES 2013-2014)

	DEHP	DINP	DIDP	DBP
DEHP		12	2	1
DINP	-		5	1
DIDP	-	-		0
DBP	-	-	-	

An analysis of cumulative risks based on biomonitoring data for six phthalates using the Maximum Cumulative Ratio. Environ Int. 112:77-84.

Worker Exposure - effects of task, shift, and season

Estimated daily intake (mg/kg/day) of (b) dibutyl phthalate (DBP), and (d) di(2-ethylhexyl) phthalate (DEHP) by industry sector using end-shift urinary phthalate metabolite concentrations. The dashed horizontal line is the U.S. EPA reference dose (RfD). The dotted horizontal line is the EFSA tolerable daily intake (TDI). In these plots, the LOD divided by two was used for observations below the LOD. Sector abbreviations: manf, phthalate manufacturing; film, PVC film, filt, vechicle filters; cmpd, PVC compounding; hose, rubber hose; boot, rubber boot; gask, rubber gasket; nail, nail-only salons.

https://www.nature.com/articles/jes200962#t2
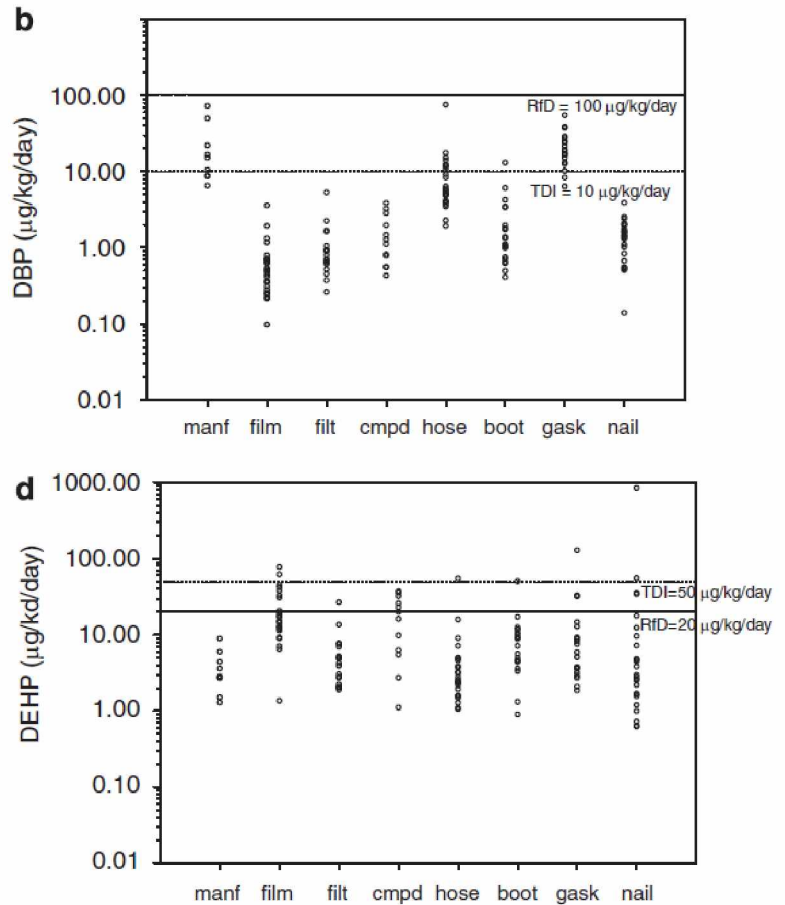
DiNP metabolite at mid-shift and end-shift in PVC film manufacturing and PVC compounding.

"Phthalate-related processes in PVC film manufacturing included compounding, mixing, paste preparation, extrusion, milling, and calendering. The PVC compounding produced custom-formulated PVC pellets with processes including mixing, extrusion, and milling."

	Sample	n	Unadjusted, µg/L		CR-adjusted, µg/g	
			GM (GSD)	Range	GM (GSD)	Range
PVC Film Manufacturing						
DiNP used on worker's TASK[a]	Mid-shift					
	Yes	7	34.4* (2.0)	15.1–77.4	14.7* (2.3)	4.45–38.9
	No (ref)	18	4.92 (2.2)	0.9–26.8	2.46 (2.2)	0.78–13.4
	End-shift					
	Yes	7	51.0* (2.4)	12.5–184	25.2* (2.1)	9.19–80.0
	No (ref.)	18	5.34 (2.8)	0.90–27.9	2.92 (2.6)	0.42–16.0
DiNP used on worker's SHIFT	Mid-shift					
	Yes	11	22.8* (2.2)	9.1–77.4	10.7* (2.2)	4.45–38.9
	No (ref.)	14	3.90 (2.1)	0.9–26.8	1.90 (1.9)	0.78–13.4
	End-shift					
	Yes	11	34.9* (2.4)	11.7–184	17.7* (2.2)	5.49–80.0
	No (ref.)	14	3.78 (2.4)	0.9–27.9	2.08 (2.1)	0.42–9.72
PVC Compounding						
DiNP used at facility[b]	Mid-shift	12	6.64 (2.4)	1.20–21.9	4.11 (2.0)	1.41–13.4
	End-shift	12	9.53** (2.3)	1.70–21.7	4.80 (2.1)	1.11–13.3

Seasonal differences: Occupational exposure to (DiNP) in polyvinyl chloride processing operations. Int Arch Occup Environ Health. 2012;85(3):317-25.

			n value	Mean	Median	5th percentile	95th percentile	SD
Summer season	General population	MEP		299.42	78.71	2.51	2025.46	594.1
		MnBP		156.04	109.27	42.06	479.21	164.93
		MiNP	31	12.65	13.63	4.6	15.26	3.3
		MEHP		19.93	18.05	9.46	32.86	7.58
	Community services	MEP	18	236.52	82.65	41.58	1452.86	371.94
		MnBP		182.73	168.53	42.73	338.95	112.14
		MiNP		7.68	4.6	4.6	16.1	4.53
		MEHP		7.22	5.64	1.87	27.13	6.48
	Plastic manufactory	MEP		663.31	84.21	40.89	5642.4	1626.37
		MnBP		225.37	151.18	35.7	741.53	218.07
		MiNP	22	15.9	14.62	12.98	21.74	3.16
		MEHP		48.85	43.64	33.75	83.64	18.98
Winter season	General population	MEP		131.82	78.3	44.11	444	143.63
		MnBP	39	97.27	85.51	38.97	257.26	61.47
		MiNP		12.22	14.1	4.6	18.05	4.69
		MEHP		28.26	27.45	0.9	77.54	23.08
	Community services	MEP		72	47.87	2.51	344.45	91.26
		MnBP		68.7	65.68	2.28	130.04	43.89
		MiNP	30	5.07	4.6	0.57	14.89	3.56
		MEHP		15.98	5.82	2.51	60.71	20.01
	Plastic manufactory	MEP		300.29	96.88	2.51	1430.43	467.81
		MnBP	15	100.55	93.79	31.17	179.47	46.53
		MiNP		10.12	12.47	4.6	18.7	4.91
		MEHP		15.98	15.79	4.54	29.8	7.58

Contribution of inhalation to phthalate exposure

Estimating the contribution of inhalation exposure to DEHP for PVC production workers, using personal air sampling and urinary metabolite monitoring (Int J Hyg Environ Health. 2014 Jan;217:102-9).

Relative cumulative frequency of daily intake of DEHP estimated using biomonitoring data of urinary metabolites and airborne DEHP exposure concentration (N = 89).
The daily intake of DEHP was 1.5-102.3 µg/kg/day for DI_{urine} and 0.01-123.0 for DI_{air}. The geometric mean of DI_{urine} (13.5) was approximately 7.5 times higher than that of DI_{air}. (1.8) (p<0.01). DI_{urine} urine median (12.5) was 25% of TDI and 64% of RfD. 9 of 89 (10%) exceeded the TDI and 26 (30%) exceeded the RfD.