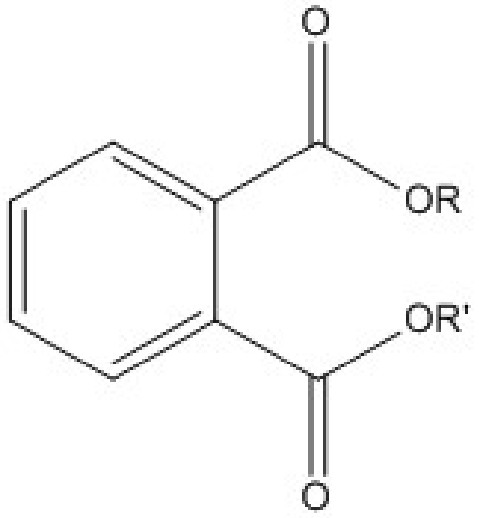
Potential designated chemicals *ortho*-Phthalates



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Safer Alternatives Assessment and Biomonitoring Section

Office of Environmental Health Hazard Assessment

Presentation to the Scientific Guidance Panel, July 16, 2015

Designated chemicals

- Chemicals that can be considered for biomonitoring by the Program
- Chemicals are designated based on:
  - Inclusion in CDC's National Reports on Human Exposure to Environmental Chemicals program
  - Recommendations by the Scientific Guidance Panel for Biomonitoring California

o-Phthalates currently on the list of designated chemicals

- Dimethyl phthalate (DMP)
- Diethyl phthalate (DEP)
- Di-*n*-butyl phthalate (DnBP)
- Di-isobutyl phthalate (DIBP)
- Benzylbutyl phthalate (BzBP)
- Dicyclohexyl phthalate (DCHP)
- Di-2(ethylhexyl) phthalate (DEHP)
- Di-*n*-octyl phthalate (DnOP)
- Diisononyl phthalate (DINP)
- Diisodecyl phthalate (DIDP)

SGP actions on *o*-phthalates

- March 2009: SGP recommended that all *o*-phthalates already designated based on CDC* be added to the list of priority chemicals

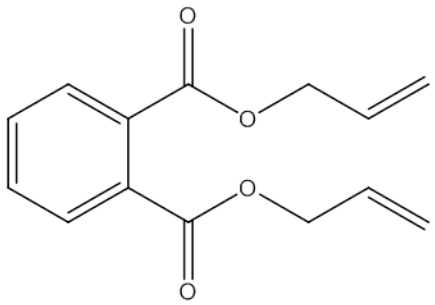
- November 2010: SGP recommended that, if new *o*-phthalates are added to the list of designated chemicals based on CDC, those should also be automatically added as priority chemicals

*Inclusion in CDC's National Reports on Human Exposure to Environmental Chemicals program

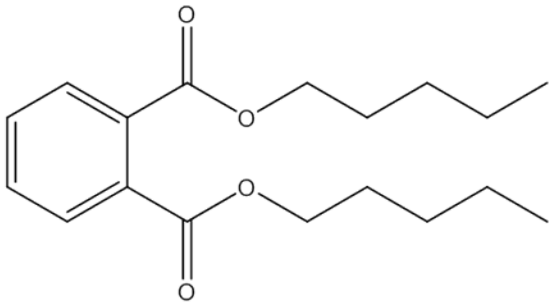
Criteria for recommending additional designated chemicals

- ***Exposure or potential exposure*** to the public or specific subgroups
- The ***known or suspected health effects*** based on peer-reviewed scientific studies
- The ***need to assess the efficacy of public health actions*** to reduce exposure to a chemical
- The ***availability of a biomonitoring analytical method*** with adequate accuracy, precision, sensitivity, specificity, and speed
- The ***availability of adequate biospecimen samples***
- The ***incremental analytical cost*** to perform the biomonitoring analysis for the chemical

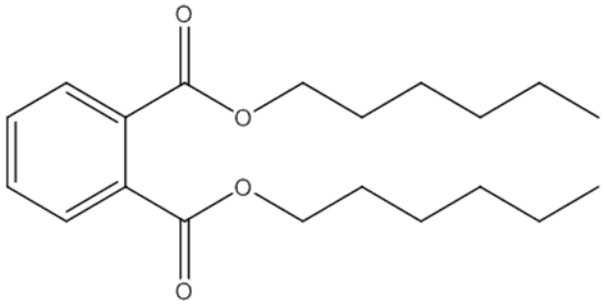
Example *o*-phthalates not currently designated



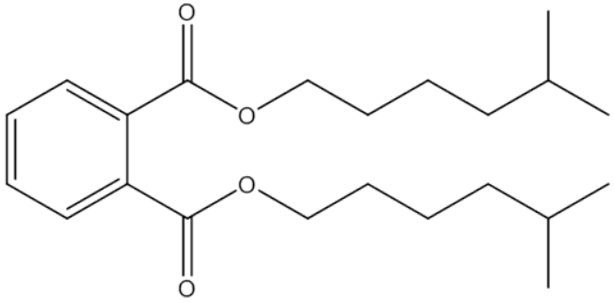
Diallyl phthalate (DAP)



Di-*n*-pentyl phthalate (DPenP)



Di-*n*-hexyl phthalate (DnHxP)



Diisoheptyl phthalate (DIHpP)
(example isomer)

Why *o*-phthalates as a class?

- *o*-Phthalates are used worldwide as plasticizers
- As certain *o*-phthalates are restricted, new *o*-phthalates may increase in use
- Limited information is available on use and human exposure for many *o*-phthalates
- Consider *o*-phthalates as a class to:
  - Facilitate broad laboratory screening for *o*-phthalates
  - Allow the Program to measure any member of the class

Restrictions on *o*-phthalates

- California restrictions:
  - DEHP, DnBP, BzBP, DnOP, DINP, and DIDP banned for use in children's toys and certain childcare articles at concentrations above 0.1% (effective January 2009)
- Similar federal restrictions on *o*-phthalates in children's toys and certain childcare articles:
  - Permanent ban on: DEHP, DnBP, and BzBP
  - Interim ban on: DINP, DIDP, and DnOP
  - Proposed rulemaking (2014):
    - Expands permanent ban to include DINP, DIBP, DPenP, DnHxP and DCHP
    - Lifts interim ban on DIDP and DnOP

o-Phthalates listed under Proposition 65

Proposition 65 listed *o*-phthalate	**Type of toxicity**			
	Developmental	Male Reproductive	Female Reproductive	Cancer
Benzylbutyl phthalate (BzBP)	✓			
Di-*n*-butyl phthalate (DnBP)	✓	✓	✓	
Di-2-ethylhexyl phthalate (DEHP)	✓	✓		✓
Di-*n*-hexyl phthalate (DnHxP)		✓	✓	
Di-isodecyl phthalate (DIDP)	✓			
Di-isononyl phthalate (DINP)				✓

Exposure or potential exposure

Some uses of *o*-phthalates

- Plasticizers that impart flexibility and durability
  - Consumer products
  - Building supplies
  - Medical equipment
  - Processing equipment for food
  - Automotive plastics
- Personal care products and cosmetics
  - As fragrance carriers in perfumes and scented products
  - To prevent brittleness and cracking in nail polish
  - As skin moisturizing, softening, and penetrating agents in lotions
  - As anti-foaming agents in aerosol products

Production/import volume

- Phthalates are still the most widely used plasticizers

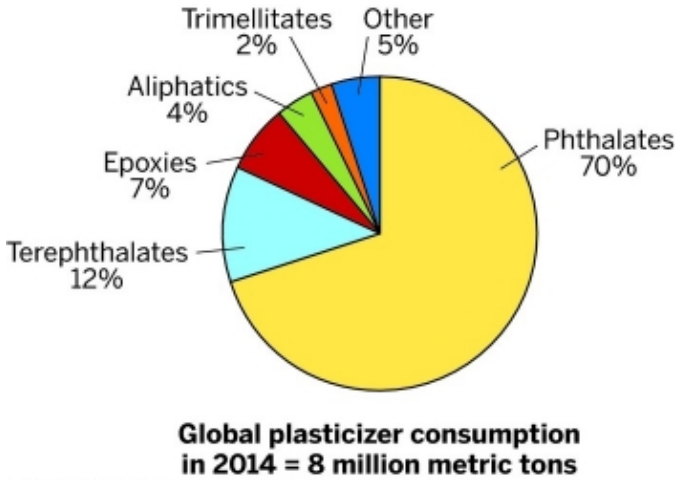


Chart from Tullo (2015)*

- US EPA (2012) database on production/import volume shows:
  - Numerous *o*-phthalates with production/import volume >1 M pounds - DEHP, DEP, DnBP, BzBP, DINP, DPHP, DUP, DIUP, and DTDP
  - Data withheld for some *o*-phthalates - for example, DAP, DIHpP, and DnOP

* http://cen.acs.org/articles/93/i25/Plasticizer-Makers-Want-Piece-Phthalates.html

Biomonitoring California results on *o*-phthalates

Parent *o*-phthalate(s)	Urinary metabolite	Detection frequency (%)			LOD (ng/mL)
		FOX (n=101)	MIEEP (n=89)	PBEST (n=109)	
Benzylbutyl phthalate (BzBP)	Mono-benzyl phthalate (MBzP)	100	100	100	0.250
Benzylbutyl phthalate (BzBP) Di-*n*-butyl phthalate (DnBP)	Mono-*n*-butyl phthalate (MnBP)	97	98	98.2	2.00
Diethyl phthalate (DEP)	Mono-ethyl phthalate (MEP)	79.2	91	97.2	8.00
Di-2-ethylhexyl phthalate (DEHP)	Mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP)	100	100	100	0.500
Di-*n*-octyl phthalate (DnOP)	Mono-3-carboxypropyl phthalate (MCPP)	98	100	100	0.125
Dicyclohexyl phthalate (DCHP)	Mono-cyclohexyl phthalate (MCHP)	4.0	3.4	1.8	0.500

LOD: Limit of detection
FOX: Firefighter Occupational Exposures (FOX) Project
MIEEP: Maternal and Infant Environmental Exposure Project
PBEST: Pilot Biomonitoring Exposures Study

Exposure trends in *o*-phthalates

- Zota et al. (2014)* analyzed US biomonitoring data from 2001-2010 and found:
  - Decreases in urinary concentrations of DEP, DnBP, BzBP, and DEHP metabolites
  - Increases in urinary concentrations of DIBP, DnOP, DINP, DIDP metabolites
- Schütze et al. (2015)* reported time trends in detections of DPHP metabolites in a study of archived urine samples from German adults:
  - Detected in 2009 and 2012, but not found in 1999, 2003, or 2006
  - Detection frequency for one DPHP metabolite increased from 3.3% in 2009 to 21.7% in 2012

*See document on *o*-phthalates for complete citations

Known or suspected health effects

- Male reproductive toxicity
  - Evidence in laboratory animals that *in utero* exposure to *o*-phthalates induces a spectrum of abnormalities of the male reproductive tract ("phthalate syndrome")
  - Anti-androgenic phthalates in approximate order of activity (CHAP*, 2014):
    - DPenP > BzBP ~ DnBP ~ DIBP ~ DnHxP ~ DEHP ~ DCHP > DINP
  - Epidemiological evidence: Decreased anogenital distance in baby boys associated with maternal *o*-phthalate exposure
- Other potential effects
  - Effects on ovary
  - Disruption of thyroid hormone homeostasis
  - Neurodevelopmental effects
  - Possible contribution to allergic disease and obesity

*Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives, convened by the Consumer Products Safety Commission

Analytical considerations

- Biomonitoring California's Environmental Health Laboratory currently measures urinary phthalate metabolites using on-line SPE–HPLC-MS/MS*
- Method currently includes ten urinary phthalate metabolites and can be expanded to include additional compounds
  - Minor incremental costs of supplies and standards
  - Additional optimization and validation required

*Solid phase extraction high performance liquid chromatography tandem mass spectrometry

Assessing efficacy of public health actions to reduce exposure

- Continued use of *o*-phthalates is expected
- For many *o*-phthalates, extent of exposure is unknown and more information is needed
- Adding the class to the list of designated chemicals would allow the Program to:
  - Choose the most important *o*-phthalates to track over time
  - Provide the necessary biomonitoring data to support the evaluation of regulatory actions on *o*-phthalates

Options for the Panel

- Recommend adding "*ortho*-phthalates" as a class to the list of designated chemicals
- Defer, pending more information
- Recommend against adding *ortho*-phthalates as class to the list of designated chemicals