Potential Designated Chemicals

Non-Halogenated Aromatic Phosphates

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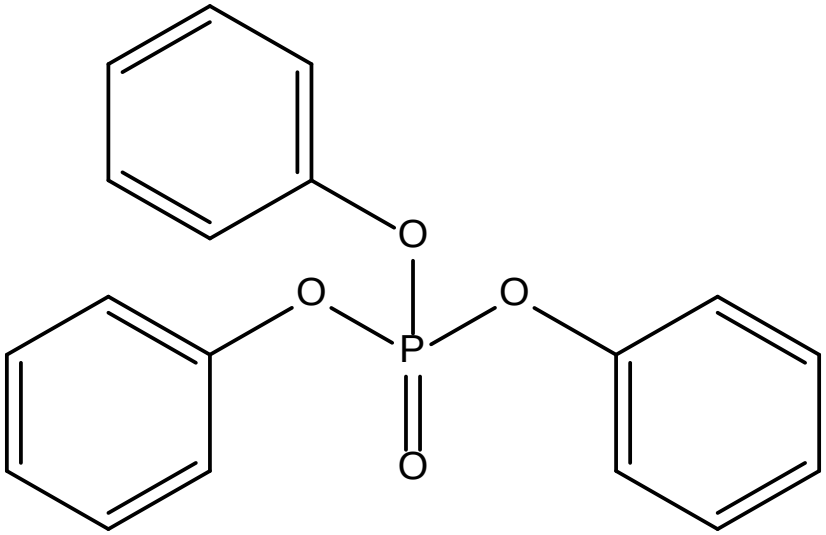
What are designated chemicals?

- Chemicals that can be considered for biomonitoring by the Program
- Consist of
  - Chemicals that are part of CDC's National Reports on Human Exposure to Environmental Chemicals program
  - Chemicals that the Scientific Guidance Panel has recommended be added to the list of designated chemicals

Background

- Triphenyl phosphate was one plasticizer presented as a possible candidate to investigate for designation (November 2010)



Background, cont.

- Screen of organophosphate flame retardants presented to SGP (March 2011)

- Panel requested that the Program prepare a potential designated document on aromatic phosphates

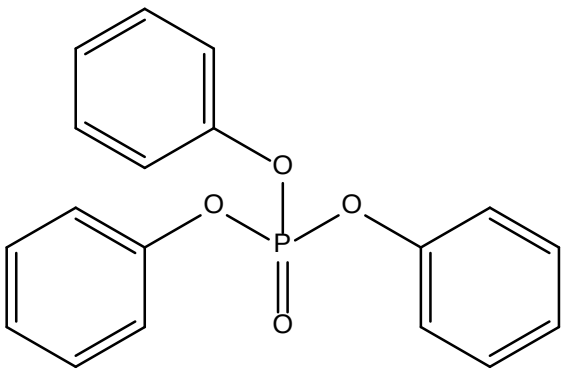
Criteria for Panel to recommend designated chemicals

- *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
- 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

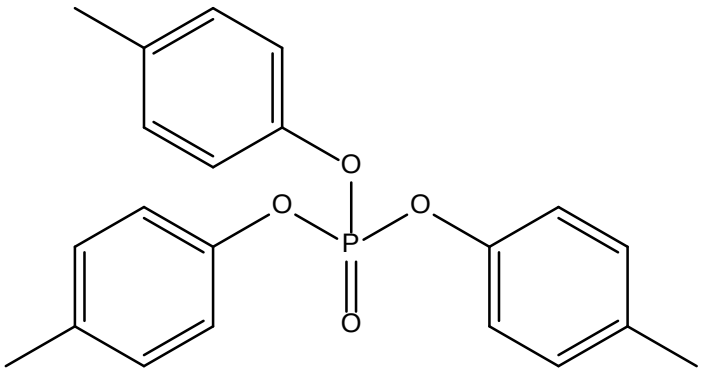
Agencies concerned about aromatic phosphates

- Consumer Product Safety Commission
- National Toxicology Program (NTP)
- EU – Environment Agency
- Others

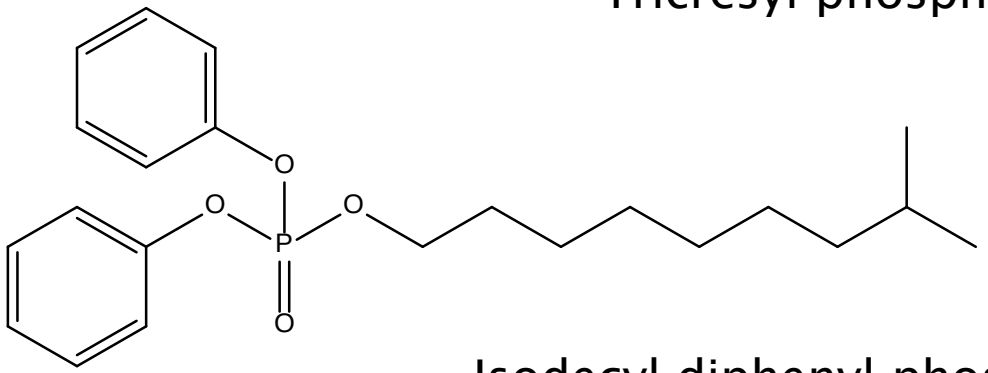
Structures to illustrate chemical class



Triphenyl phosphate

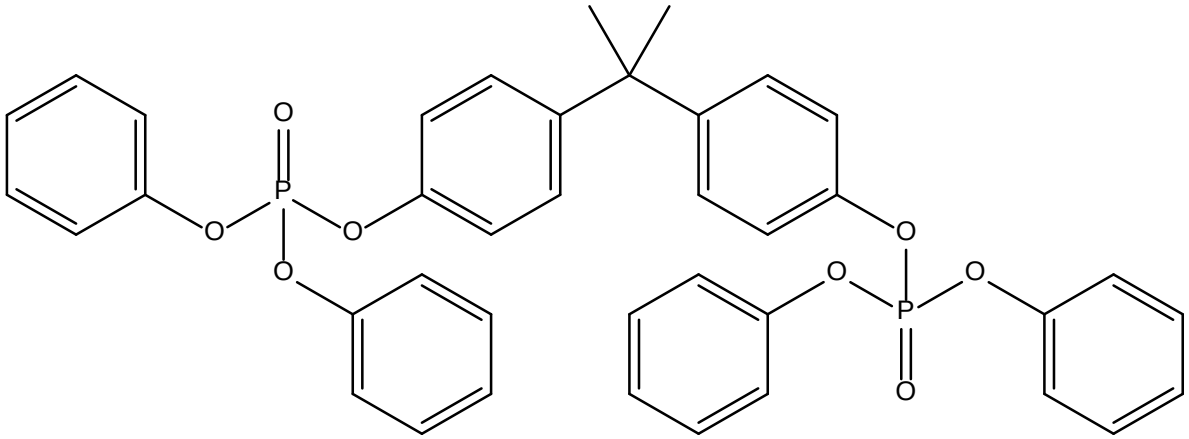


Tricresyl phosphate (para)

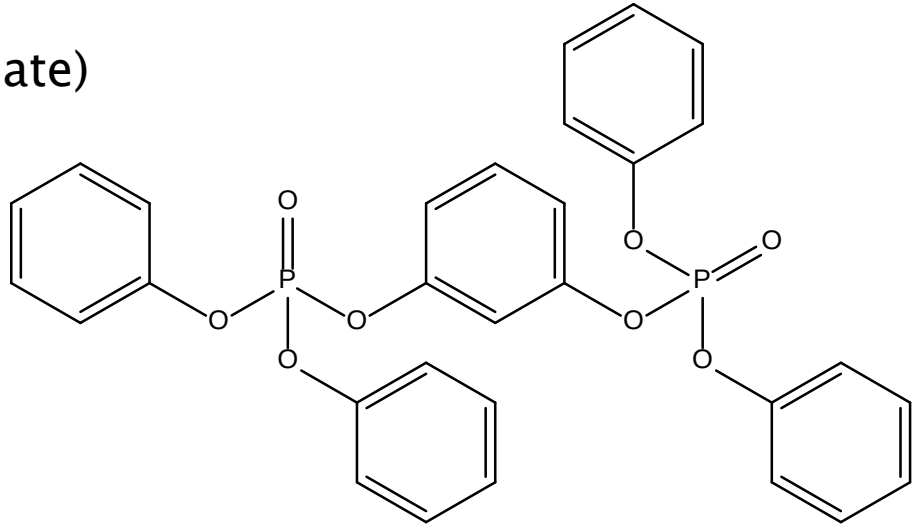


Isodecyl diphenyl phosphate

Structures, cont.



Bisphenol A bis(diphenyl phosphate)



Resorcinol bis(diphenyl phosphate)

Uses: Flame retardants & plasticizers

- PVC and other plastics –consumer electronics
- Polyurethane foam
- Textiles – backcoatings and artificial leather
- Paints and varnishes
- Hydraulic fluids

Examples of flame retardant uses in plastics

- TVs – in housing, replacing decaBDE
  - Bisphenol A bis(diphenyl phosphate)
  - Resorcinol bis(diphenyl phosphate)
  - Triphenyl phosphate

- Computers – screens, keyboards, printers, mouse

Flame retardant uses: Polyurethane foam

- U.S. Consumer Product Safety Commission staff concerns about increasing use of aromatic phosphates in furniture foam

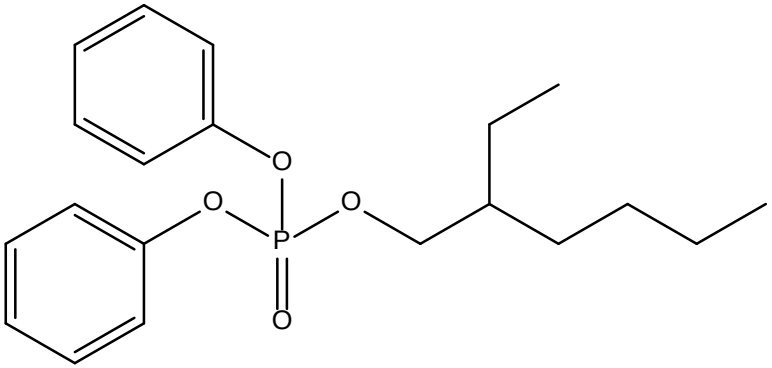
Found in foam:

- Isopropylated triphenyl phosphate
- Triphenyl phosphate
- Butylated triphenyl phosphate

Plasticizer uses: Food contact packaging

Ethylhexyl diphenyl phosphate

- Candy caramels – 2.47 µg/g (mean)
- Margarine –1.2 µg/g (mean)
- Bread – 0.1 µg/g (mean)



Other household/consumer uses

- Curtains
- Upholstery fabric
- Wallpaper
- Nail polish
- Dog flea collars
- Biodegradable tampon ejectors
- Tubings for skinless sausages

Levels identified in house dust

Aromatic Phosphate	% Detect	Median (Range) µg/g	Study
Triphenyl phosphate			
Belgium	100	0.50 (0.04–29.8)	Van den Eede et al. (2011)
Boston MA	98	5.5 (nd – 1800)	Stapleton et al. (2009)
Tricresyl phosphate			
Belgium	97	0.24 (<0.04–5.07)	Van den Eede et al. (2011)

nd = non-detect

Levels identified in dust

Chemical	Median (range) µg/g		
	Home	Office	Day care
Ethylhexyl diphenyl phosphate	0.5 (nd–1.8)	1.0 (nd–73)	0.8 (0.2–160)
Triphenyl phosphate	1.2 (0.1–4.2)	5.3 (0.9–32)	1.9 (0.3–17)

Bergh et al. (2011)

Comparison of flame retardants in house dust

Flame Retardant	Measured in house dust		
		µg/g	nmoles/g
Triphenyl phosphate (n=50)	GM	7.36	22.6
TDCPP [Tris(1,3-dichloro-2-propyl) phosphate] (n=50)	GM	1.89	4.4
PBDEs (n=24)			
BDE-47	GM	0.577	1.2
BDE-99	GM	0.809	1.4

GM = geometric mean

Stapleton et al. (2009)
Meeker et al. (2009)

Known or suspected health effects

- Bisphenol A bis(diphenyl phosphate)
  - Possible metabolism to bisphenol A and bisphenol A diphenyl phosphate
  - Biological activity of bisphenol A diphenyl phosphate not known

- Butylated triphenyl phosphate
  - On Grandjean and Landrigan's list of chemicals neurotoxic to humans

Known or suspected health effects

- Isopropylated triphenyl phosphate
  - Neurotoxicity in hens
  - *In vitro*: effect on human androgen receptor activity; activation of two human nuclear receptors (CAR, PXR)
- Tricresyl phosphate
  - Neurotoxicity – *o*–tricresyl phosphate
  - Reproductive toxicity
  - Effects on adrenal cortex
  - *In vitro*: *p*–tricresyl phosphate activation of two human nuclear receptors (CAR, PXR)

Known or suspected health effects

- Triphenyl phosphate
  - Levels in house dust associated with decreased sperm concentration and increased prolactin in men (n=50) recruited from an infertility clinic
  - On Grandjean and Landrigan's list of chemicals neurotoxic to humans
  - *In vitro* studies: effect on human androgen receptor activity; activation of human nuclear receptors (CAR, PXR)

Planned NTP Studies

Six representative non-halogenated aromatic phosphates to be studied.

- *In vivo* studies on two aromatic phosphates
  - Modified one-generation study in rats
    Neurotoxicity, immunotoxicity, reproductive/developmental
  - Studies in adult mice

- *In vitro* studies: neurotoxicity, reproductive toxicity, effects on liver enzymes and steroidogenesis

Physical chemical properties

- For most, pure chemical was not evaluated
  - Contamination with triphenyl phosphate
  - Other components of mixture
  - Mixtures of isomers
- Range of vapor pressures identified
  - E.g., Bisphenol A bis(diphenyl phosphate) – $< 9 \times 10^{-6}$ to 1.5×10^{-4}
- Log octanol–water partition coefficient (log K_{ow})
  - Evidence of bioaccumulation potential: log $K_{ow} \geq 4$
  - Most aromatic phosphates ranged from 4.6 to 6.6

Persistence – Predictions using PBT Profiler*

Chemical	Meets EPA criteria for P and vP		
	Sediment	Soil	Water
Bisphenol A bis(diphenyl phosphate)	vP	P	P
t-Butylphenyl diphenyl phosphate	vP	P	
Ethylhexyl diphenyl phosphate	P		
Isodecyl diphenyl phosphate	vP	P	
Tris(isopropyl phenyl) phosphate	vP	P	P
Isopropylphenyl diphenyl phosphate	vP	P	
Resorcinol bis(diphenyl phosphate)	vP	P	
Tricresyl phosphate	vP	P	
Triphenyl phosphate	vP	P	

***U.S. EPA screening tool**

P = persistent
vP = very persistent

Bioaccumulation

- Findings in biota
  - Triphenyl phosphate – dolphins, fish, bivalves
  - Ethylhexyl diphenyl phosphate – fish
- Bioconcentration factors (BCFs)
  - BCF > 1000 – bioaccumulation potential
  - BCFs for some aromatic phosphates

Tris(isopropyl) phenyl	1986
Ethylhexyl diphenyl	1600
Isodecyl diphenyl	1100
Isopropylphenyl diphenyl	970
Triphenyl	420
Bisphenol A bis(diphenyl)	3

Pharmacokinetics and metabolism

- Oral absorption
- Urinary metabolites identified for some chemicals
- Route of excretion may vary with isomer
  - *o*–Tricresyl phosphate, urine
  - *m*–Tricresyl phosphate, feces
  - *p*–Tricresyl phosphate, dose-dependent
- Triphenyl phosphate and ethylhexyl diphenyl phosphate detected in breast milk
- More research needed to determine which phosphates would be found in urine or blood

Biomonitoring studies

- Urine
  - Triphenyl phosphate metabolite (diphenyl phosphate)
    - United States (n=9):
      Median: 1.8 µg/L, Range: 0.569 – 63.8 µg/L
    - Germany (n=19):
      Median: 1.3 µg/L, 95th percentile: 28.6 µg/L

- Breast milk (Sweden, pooled samples)
  - Triphenyl phosphate: Median: 8.5 ng/g lipid
  - Ethylhexyl diphenyl phosphate: Median: 6.5 ng/g lipid

Laboratory analysis

- Biomonitoring California would need to adapt/develop analytical methods
  - Methods for analysis of diphenyl phosphate in urine are available in the literature
- Reference standards available for only a few aromatic phosphates
- Analysis of non-halogenated aromatic phosphates could likely be bundled

Need to assess efficacy of public health actions

- Widespread and probable increasing use of non-halogenated aromatic phosphates

- Biomonitoring would:
  - Help assess extent and level of exposure in California
  - Evaluate the need for further action

Options for the Panel

- Consider designating:
  - "Non-halogenated aromatic phosphates" as a class
  - Individual chemicals (e.g., triphenyl phosphate)
- Consider later, with more information:
  - Pending results from NTP studies, other toxicity or exposure information
- Decide against designating