Chronic Hazard Advisory Panel (CHAP) on Phthalates and Phthalate Substitutes

U.S. Consumer Product Safety Commission
Bethesda, MD, USA
April 14-15, 2010

These comments are those of the CPSC staff, have not been reviewed or approved by, and may not necessarily reflect the views of, the Commission.
Agenda

- Welcome
- Background & History
- Overview of Phthalates Chemistry & Toxicity
- 2010 CHAP on Phthalates
  
  Break
- Election of Chair & Vice-Chair
- CHAP Deliberations Begin
# 2010 CHAP on Phthalates

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
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<tbody>
<tr>
<td>Chris Gennings, PhD</td>
<td>Medical College of Virginia</td>
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<tr>
<td>Holger M. Koch, PhD</td>
<td>Ruhr University of Bochum</td>
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<tr>
<td>Paul J. Lioy, PhD</td>
<td>Robert Wood Johnson Medical School</td>
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<td>Bernard A. Schwetz, DVM, PhD</td>
<td>U.S. Department of Health and Human Services (retired)</td>
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<td>Russell Hauser, MD, ScD, MPH</td>
<td>Harvard University SPH</td>
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<tr>
<td>Andreas Kortenkamp, PhD</td>
<td>University of London</td>
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<tr>
<td>Philip E. Mirkes, PhD</td>
<td>Washington State University</td>
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<td>Vancouver</td>
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Background & History of Phthalates
Activities at CPSC

April 14, 2010

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Di(2-Ethylhexyl) Phthalate (DEHP) in Children’s Products—1980’s

- National Toxicology Program (NTP) found liver tumors in mice & rats
- CPSC initiated rulemaking process
- Chronic Hazard Advisory Panel (CHAP)
- Voluntary ban in teethers, rattles, and pacifiers (1985)
  - Later incorporated by ASTM F-963
- DEHP replaced by DINP
Diisononyl Phthalate (DINP) in Children’s Products

- CPSC petitioned to ban PVC in children’s products (1998)—Phthalates, Pb, Cd
- Phthalates voluntarily removed from teethers & rattles (1999)
- To assess the potential DINP risk, CPSC:
  - Convened a CHAP
  - Study of children’s mouthing activity
  - Laboratory method for DINP migration
**DINP in Children’s Products**

- **CHAP (2001)**
  - Cancer risk was “negligible or non-existent”
  - DINP posed a “minimal to non-existent risk” based on chronic liver toxicity

- **CPSC:** DINP in soft plastic toys, teethers, & rattles not hazardous to children (2002)

- Petition to ban PVC in children’s articles denied

- One phthalate; one source of exposure
Consumer Product Safety Improvement Act (CPSIA) Section 108

• Effective February 2009
• Permanent Ban
  – DBP, BBP, and DEHP (>0.1%)
  – Children’s toys and child care articles
• Interim Ban—Pending Review by CHAP
  – DINP, DIDP, DNOP (>0.1%)
  – Children’s toys that can be placed in a child’s mouth and child care articles
• CHAP on Phthalates & Substitutes
Overview of Phthalates Chemistry and Toxicity

April 14, 2010

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Dialkyl \( o \)-Phthalates (\( o \)-DAP’s)

- \( \geq 30 \) Commercial \( o \)-DAP’s
- Metabolites of 10 \( o \)-DAP’s detected in human urine
- \( \sim 90\% \) used as PVC plasticizers
- \( \sim 10\% \) as plasticizers for other plastics, solvents (esp. diethyl & dimethyl)
- Viscous liquids, hydrophobic, low vapor pressure
- Physico-chemical properties—carbon backbone length, branching—affect uses & biological effects
Types of Dialkyl \( o \)-Phthalates

- **Short-chain/low molecular weight**
  - Dimethyl, diethyl
  - Solvents, plasticizers for cellulosics

- **Transitional/medium weight**
  - Dibutyl, butylbenzyl, DEHP
  - Solvents or PVC plasticizers

- **Long-chain/high weight**
  - DINP, DIDP
  - PVC plasticizers
Branched and Linear Phthalates

- *Iso*-alcohols
  - >6 carbons \(\equiv\) mixture of isomers
  - DINP, DIDP
  - Multiple processes yield different mixtures, & unique CAS numbers

- Linear alcohols may contain significant amounts of branched chain impurities
  - Branched chain alcohols may contain significant amounts of straight chain impurities
$\omega$-DAP $\rightarrow$ Monoester $\rightarrow$ Phthalic Acid

$\omega$-1 Hydroxy-Monophthalate

$\omega$-Carboxy-Monophthalate

$\omega$-1 Oxo-Monophthalate
Toxicity of $\alpha$-DAP’s

- Acute toxicity; skin & eye irritation, sensitization—generally low; not genotoxic
- Focus on chronic/subchronic effects
- Liver & kidney most common targets
- PPAR$\alpha$
  - Peroxisome proliferation; liver tumors
  - May be required for some toxic effects
- Other tumors—MNCL, testes, kidney
- Reproductive/developmental effects
## Target Organs for Selected o-DAP’s

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PPARα Activation *In Vitro*

Bility et al. 2004

Fold Induction

Increasing Molecular Weight →

Mouse / Human
Peroxisome Proliferation *in Vivo*

Barber et al. 1987
F344 Rat

Relative PCOA Activity

Increasing Molecular Weight →

- DBP
- BBP
- 610P
- DEHP
- DINP
- 711P
- DIDP
- DUP
“Phthalate Syndrome”

• Certain phthalates inhibit testosterone production in rodents
• Profound effects in male pups during late gestation ("perinatal exposure")
  – Juvenile & adult males & female fetus less sensitive
• Linear C3 – C6 o-DAP’s or branching at C2
• Effects of multiple o-DAP’s are additive
  (Howdeshell et al. 2008)
# Phthalates Syndrome (2)

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<tr>
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<td>Di-<em>n</em>-propyl phthalate</td>
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<tr>
<td>Di(2-ethylhexyl) phthalate</td>
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<tr>
<td>Diisononyl phthalate</td>
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Epidemiological Studies

- Duty et al. 2003, 2004; Jonsson et al. 2005
  - Effects on semen quality
- Swan et al. 2005
  - Reduced anogenital distance (AGD)
- Main et al. 2006
  - Cryptorchidism (no association)
  - Hormone levels
- Zhang et al. 2009
  - Reduced birth weight
- Suggestive, but no causal link
  - Confounded by multiple phthalate exposures
Biomonitoring Data

- Urinary Metabolites
  - Robust data for general population
  - Limited data for children < 3 years old, expectant mothers
  - 10 Phthalates, 21 metabolites

- NHANES

- National Children’s Study
  - To obtain data from conception through childhood

- Biomonitoring studies in Canada & Europe
Sources of Exposure

- **Food**—Background, processing, packaging
- **Personal care products** (lower MW)
- **Medical devices** (DEHP)
  - Subpopulation
- **Automobile Interiors**
- **Consumer Products**
  - Home furnishings, fragrance products
  - Children’s products (pre-CPSIA)
- **Environment**
  - Ambient air, indoor air, water, household dust
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Chronic Hazard Advisory Panel (CHAP)

- Consumer Product Safety Act (CPSA)
- Cancer, birth defects, & gene mutations
- Seven independent scientists who:
  - Selected by CPSC from a list of $\geq 21$
  - Possess the required expertise
  - Not employed by the federal government, except NIH, NTP, or NCTR
  - Not associated with manufacturers
- Members select a Chair and Vice-Chair
2010 CHAP on Phthalates

For all phthalates used in children’s products:

- All potential effects on children’s health
  - Including endocrine disruption
- Individual and cumulative risks
- Estimate exposure to children, pregnant women, and others
- Total phthalate exposure from:
  - Children’s products
  - Personal care products
  - All other sources
- All routes of exposure
CHAP’s Examination

- Level of no harm to:
  - Children
  - Pregnant women
  - Other susceptible individuals
  - Offspring
  - Using appropriate safety factors
- Phthalate alternatives used in children’s products
- Conducted *de novo* using
  - All available information
  - Objective methods
CHAP Report

- CHAP Report
  - Includes a recommendation whether to ban any additional phthalates or phthalate alternatives.

- CPSC Staff
  - Evaluate CHAP report and recommend whether to ban any additional phthalates or phthalate alternatives.
  - Recommend to the Commission whether to make the interim ban permanent
Timeline

- The CHAP has 18 months to complete its examination, and
- 6 Months to prepare a final report
- CPSC staff has 6 months to prepare a Commission briefing package (2012)
CPSC Staff Activities

- Toxicity reviews of 6 phthalates
  - DBP, DBP, DEHP, DINP, DIDP, DNOP
- Toxicity reviews of 5 phthalate alternatives
  - ATBC, DEHA, DINCH, DEHT/DOTP, TOTM
- Review of published exposure data
- Lab study on plasticizers in children’s toys
  - ID, concentration, & migration
- Coordinate with federal agencies
  - FDA, CDC, EPA, National Children’s Study
Phthalate Substitutes

• Potentially very many
  – Non-regulated o-DAP’s, terephthalates

• Reviewed toxicity for 5 candidates
  – Acetyl tributyl citrate (ATBC)
  – Di(2-ethylhexyl) adipate (DEHA)
  – Diisononyl 1,2-dicarboxycyclohexane (DINCH)
  – Di(2-ethylhexyl) terephthalate (DEHT)
  – Trioctyl trimellitate (TOTM)
Interagency Coordination

CHAP’s review crosses jurisdictions

- FDA—Cosmetics, food & food packaging, medical devices, drugs
- EPA—Ambient & indoor air, water
- CPSC—Household furnishings, building materials, wire & cable, toys
- DOT—Automobile interiors
- CPSC will request available data from other federal agencies
- International activities—Canada, Germany
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