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

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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

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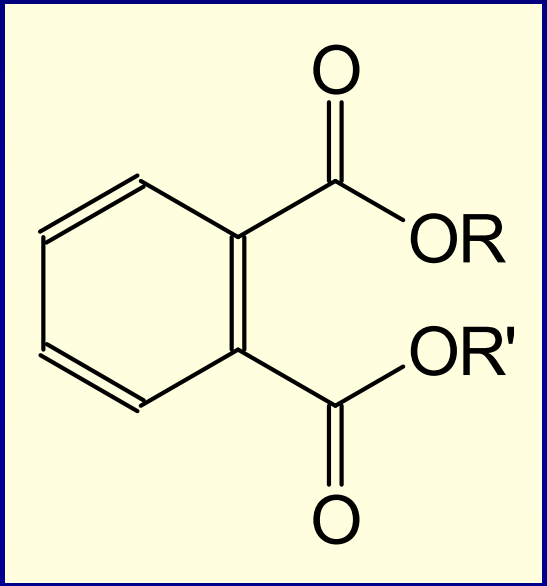
Dialkyl *o* -Phthalates (*o* -DAP's)

- ≥ 30 Commercial *o*-DAP's
- Metabolites of 10 *o*-DAP's detected in human urine
- ~90% used as PVC plasticizers
- ~10% as plasticizers for other plastics, solvents (esp. diethyl & dimethyl)



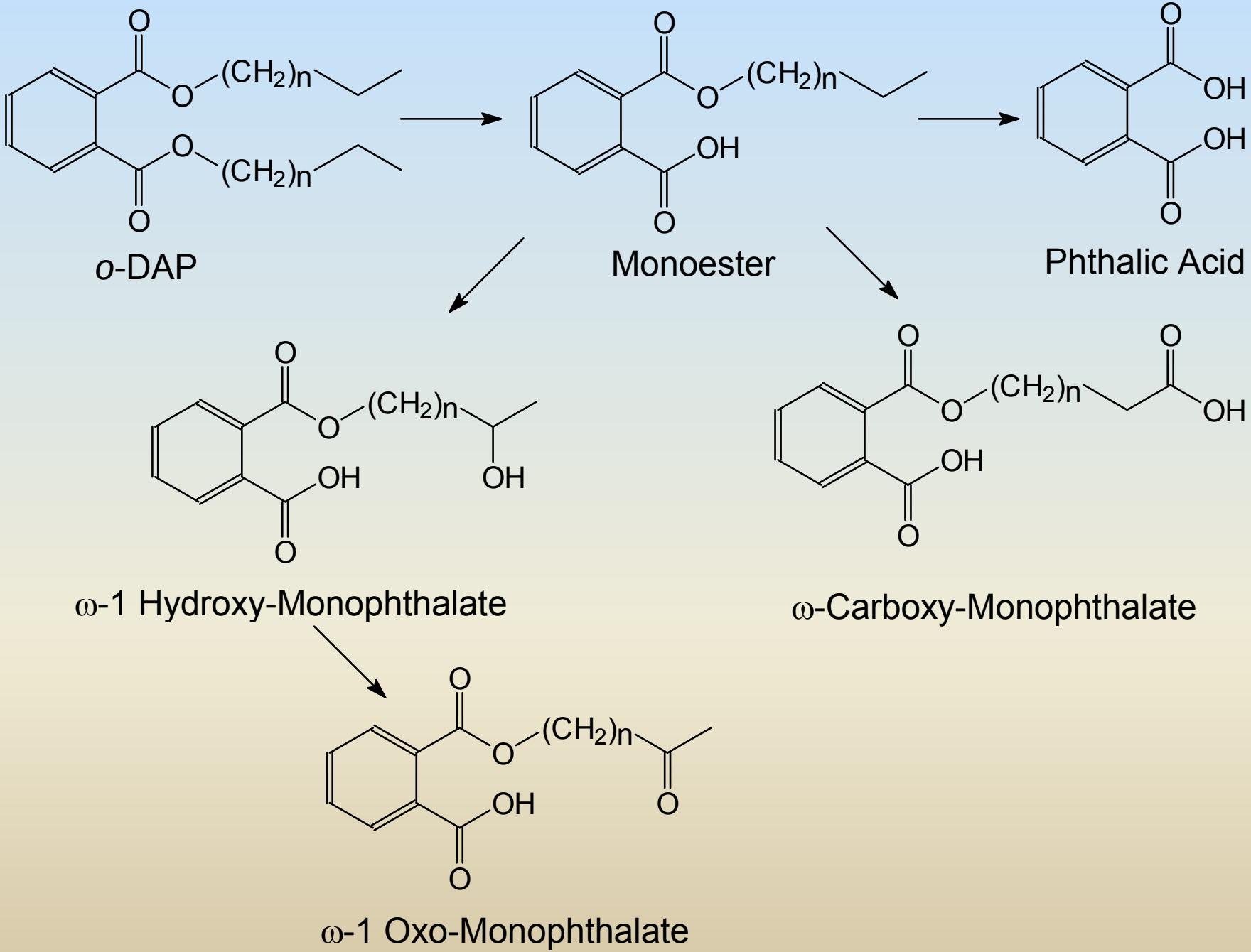
- Viscous liquids, hydrophobic, low vapor pressure
- Physico-chemical properties—carbon backbone length, branching—affect uses & biological effects

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 ≡ 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


o-DAP
Monoester
Phthalic Acid
ω-1 Hydroxy-Monophthalate
ω-Carboxy-Monophthalate
ω-1 Oxo-Monophthalate

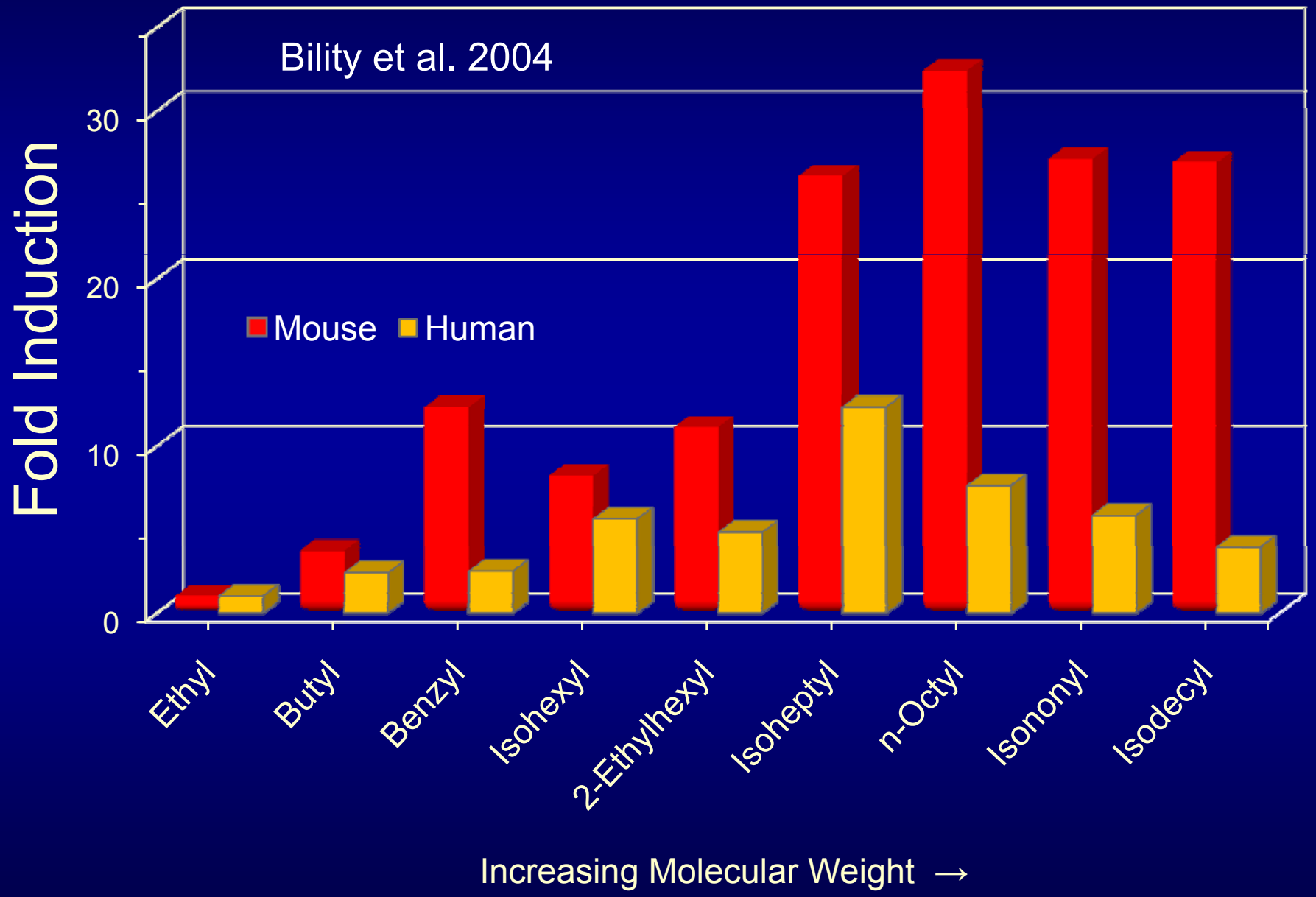
Toxicity of *o*-DAP's

- Acute toxicity; skin & eye irritation, sensitization—generally low; not genotoxic
- Focus on chronic/subchronic effects
- Liver & kidney most common targets
- PPARα
  - Peroxisome proliferation; liver tumors
  - May be required for some toxic effects
- Other tumors—MNCL, testes, kidney
- Reproductive/developmental effects

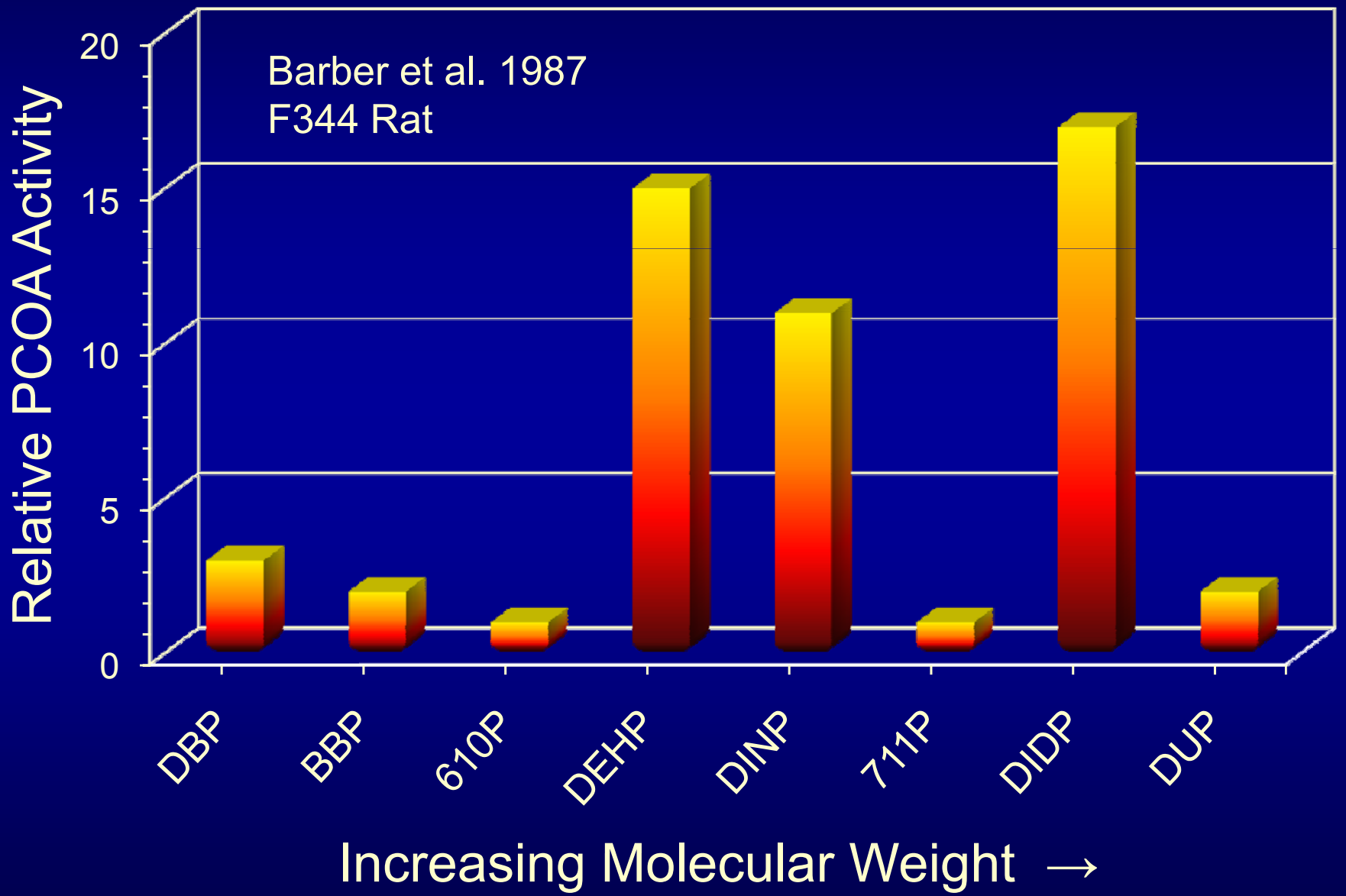
Target Organs for Selected *o*-DAP's

	Liver	Kidney	Testes	PPAR	Repro	Dev	Genetox	Tumor
DMP	✓	✓	--	?	?	--	--	?
DEP	✓	✓	--	--	✓	+/-	--	?
DBP	✓	✓	✓	✓	✓	✓	--	?
BBP	✓	✓	✓	✓	✓	✓	--	--
DNOP	✓	--	--	✓	--	✓	--	?
DEHP	✓	✓	✓	✓	✓	✓	--	✓
DINP	✓	✓	✓	✓	--	✓	--	✓
DIDP	✓	✓	--	✓	--	✓	--	--

PPARα Activation *In Vitro*



Peroxisome Proliferation *in Vivo*



“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)

Active

Di-*n*-propyl phthalate

Di-*n*-butyl phthalate

Di-*n*-pentyl phthalate

Di-*n*-hexyl phthalate

Di-*iso*-butyl phthalate

Di-*sec*-butyl phthalate

Butyl benzyl phthalate

Di(2-ethylhexyl) phthalate

Diisononyl phthalate

Inactive

Di-*n*-heptyl phthalate

Dimethyl phthalate

Diethyl phthalate

Di-*n*-octyl phthalate

Di-*t*-butyl phthalate

Terephthalates, isophthalates

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 ≥ 21 nominated by National Academy of Sciences
  - 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 has18 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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