Role of Epidemiology in Risk Assessment: A Case Study of Fiveortho-Phthalates

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Collaborative on Health and the Environment
Hazards associated with plastic packaging: overview of plastic packaging materials.

DICHLOROETHYL PHthalate (DCP)
DIOETHYLPHthalate (DEP)
DIISOBUTYL PHthalate (DIBP)
BENZYL BUTYL PHthalate (BBP)

63 chemicals in the database of chemicals with high concern and/or high reproductive toxicity.

Criteria:
- Presence in human body
- High concern or high reproductive toxicity

Priority: human health

Hazards of chemicals in packaging associated with human health.

63 chemicals --> 5 chemicals of concern:
- e.g., substance of very high concern
- Regulatory status under REACH:

Prioritization of chemicals in plastic packaging project.
Regulatory agencies establish so-called ‘safe levels’ the amount of each chemical above which the risk to human health increases. We refer to them as Reference dose (RfD).

Regulatory agencies establishing so-called ‘safe levels’ the amount of:

UC Consumer Protection Safety Commission (CPSC)
US Food and Drug Administration (US FDA)
US Environmental Protection Agency (US EPA)
European Food Safety Authority (EFSA)
European Chemical Agency (ECHA)

Phthalates are regulated in materials such as paper, paperboard and plastic adhesives, lubricants, binders, coating agents, defoamers, gasket closures, and BBP, DBP, DIDP, DEHP and DCHP uses are regulated including: plasticizers.
Kilogram or body weight per day

All units are in microgram per

0.1% (w/w)

children articles at levels above

allowed in children toys and

the United States, DCHP is not

we didn’t find an Rfd for DCHP. In

the male reproductive system.

The Rfds were based on toxicity to

Based on animal studies

for Four Phthalates

Current ECfA Rfd

<table>
<thead>
<tr>
<th>Endpoint and effect of Phthalate</th>
<th>Rfd (μg/kg-day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEHP</td>
<td>35</td>
</tr>
<tr>
<td>DBP</td>
<td>6.7</td>
</tr>
<tr>
<td>BBP</td>
<td>500</td>
</tr>
<tr>
<td>DIBP</td>
<td>8.3</td>
</tr>
</tbody>
</table>

Reference of 25% between DIBP to DBP; possible potency difference overall potency of DIBP similar from various studies and several other endpoints reduced anginal distance in adult male offspring and mammary gland changes at 21 weeks postnatal day, reduced spermatocyte development and reduced testes weight testicular germ cell depletion.
Phthalates are the everyday chemicals. They are part of our daily life.
What are the levels of health effects on human data for more than 60 years in commerce and in particular these have been...
Goal: To investigate whether regulatory safe levels (RfD) of phthalates are protective of adult outcomes in addition to male reproductive health.

Development of this pathway to improve the health and well-being of future generations.
of phthalate needed to observe that effect associated with and effect and back-calculated the dose or amount identified lowest phthalate concentration statistically significantly

## Intake Estimation

be statistically significant endpoint: (2) association between concentration and endpoint must
concentration in any bodily fluid; (2) description of a measured studies must have data on any of the 5 phthalates including (1)

## Criteria for Inclusion

studies+metabolites+biomonitoring+children+pregnant women+
combination with human exposure+epidemiological
search terms included chemicals full names, CASRN, synonyms in

## Targeted Literature Search

What we did
What we found

- Metabolic
- Hormonal
- Behavioral
- Neurodevelopmental
- Reproductive (male and female)

Endpoints associated with the following metabolites showed significant DEHP, DBP, BBP, and DIBP.

DCHP

- None of the studies evaluated
- Assessed DEHP was the most frequently
- All reported urinary metabolites
- Population-wide, small cohorts
- Cross-sectional, longitudinal

Out of 64 publications met our criteria.
<table>
<thead>
<tr>
<th>Population Tested</th>
<th>Estimated Intake</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (12 yo)</td>
<td>0.19</td>
<td>Increased</td>
<td>[72]</td>
</tr>
<tr>
<td>Children (8-14 yo)</td>
<td>0.18</td>
<td>Decreased</td>
<td>[70, 53]</td>
</tr>
<tr>
<td>Children (12 yo)</td>
<td>0.18</td>
<td>Decreased</td>
<td>[72]</td>
</tr>
<tr>
<td>Mothers 3T</td>
<td>0.17</td>
<td>Decreased and Decreased</td>
<td>[66]</td>
</tr>
<tr>
<td>Women</td>
<td>0.13</td>
<td>Decreased</td>
<td>[39]</td>
</tr>
<tr>
<td>Children (4-9 yo)</td>
<td>0.10</td>
<td>Decreased</td>
<td>[71]</td>
</tr>
<tr>
<td>Mothers 2T</td>
<td>0.08</td>
<td>Decreased</td>
<td>[72]</td>
</tr>
<tr>
<td>Mothers 3T</td>
<td>0.07</td>
<td>Decreased</td>
<td>[64]</td>
</tr>
<tr>
<td>Mothers 3T</td>
<td>0.06</td>
<td>Increased</td>
<td>[50]</td>
</tr>
<tr>
<td>Women</td>
<td>0.03-0.16 d</td>
<td>Decreased</td>
<td>[39]</td>
</tr>
</tbody>
</table>

Table 3: Ten lowest estimated intakes were associated with effects in women and children.

What we found
What we found

- Times lower than RFD
- Effects were 8000-5000

- Greater than RFD
- Estimate was ~7-times
- The highest intake

For DEHP

- Their RFD
- Effects were below
- Associated with health
- Ranges of intake

For DBP, BBP and DIBP
<table>
<thead>
<tr>
<th>Significant endpoint</th>
<th>Highest intake</th>
<th>Estimated DBP (μg/kg/day)</th>
<th>Lowest intake</th>
<th>Estimated DBP (μg/kg/day)</th>
<th>RfD Phthalate</th>
<th>Endpoint and effect of Phthalate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased occurrence of eczema in children [53]</td>
<td>0.51</td>
<td>0.08</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased body mass index in men and women [51]</td>
<td>0.58</td>
<td>0.06</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Decreased number of ovarian follicles in women [39]</td>
<td>2.42</td>
<td>0.03</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Decreased sperm motility and fertility in men [47]</td>
<td>2.86</td>
<td>1.19</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased sperm concentration in men [48]</td>
<td></td>
<td>0.03</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Increased binding globulin in children</td>
<td></td>
<td>0.08</td>
<td></td>
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</tr>
<tr>
<td>Decreased masculine play in boys [52]</td>
<td></td>
<td>0.08</td>
<td></td>
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<td></td>
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<tr>
<td>Increased thyroid hormone concentration in men</td>
<td>0.67</td>
<td>0.03</td>
<td></td>
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</tr>
<tr>
<td>Decreased seminal quality and function [49]</td>
<td>2.1</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Units are in microgram per kilogram of body weight per day.
Prenatal exposures

Health effects in children

- Decreased masculine behavior
- Increased odds of ADHD
- Externalization, withdrawn personalities
- Behavioral changes: delinquency
- Executive development
- Decreased intellectual, memory and development
- Delayed psychomotor and mental
Waist circumference, weight
Fat tissue: body mass index,
TSH (children and adults)
Thyroid: decrease T4, T3,
Pancreas: insulin resistance

**Metabolic health effects**
Reduced anogenital distance

Imbalanced hormone levels

Decreased level of male hormones count

Decreased semen quality, sperm count

Delayed puberty

Decreased number fertilized eggs

Reduced number antral follicles

Reproductive health effects
Epidemiology data show health effects not commonly assessed in toxicity studies. Effects were observed at levels much lower than current RfDs are not bright lines between no risk/risk; it's more complex. There is substantial human evidence assessed in toxicity studies. RfDs are not bright lines between no risk/risk; it's more complex.

A dialogue between regulators, the medical community, and academic researchers must be established. Scientific knowledge and market behavior are dynamic. Safety evaluations must also be

Summary and Conclusions
The bookends of environmental health must establish a more fluent dialogue that involves the people, the practitioners, and the regulators.
Until a profound modernization of the risk assessment and management of chemicals occurs, human studies should be taken into account to identify whether the health risk of chemicals in commerce should be reassessed.