







Role of epidemiology in risk assessment: a case study of five ortho-phthalates

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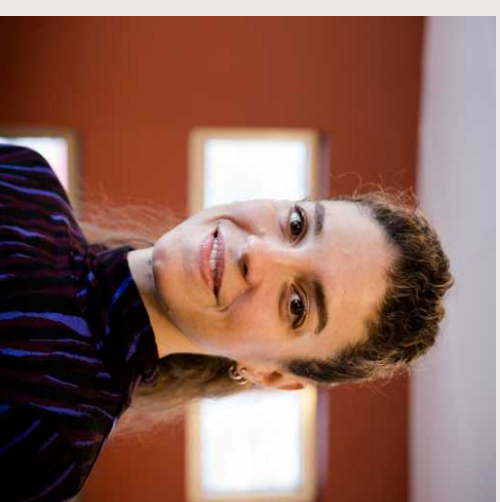
Food Packaging
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Hazardous chemicals in plastic packaging project

Database of chemicals associated with plastic packaging

Prioritization of chemicals hazardous to human health

Phthalates

BENZYL BUTYL PHTHALATE (BBP)
DIBUTYL PHTHALATE (DBP)
DIISOBUTYL PHTHALATE (DIBP)
DIETHYLBEXYL PHTHALATE (DEHP)
DICYCLOHEXYL PHTHALATE (DCHP)

OVERVIEW OF PLASTIC PACKAGING-ASSOCIATED CHEMICALS AND THEIR HAZARDS
Of the 906 chemicals likely associated with plastic packaging, **63 rank highest for human health hazards**

- Criteria:
- Present in the human body
 - Regulatory status under REACH; e.g., substance of very high concern
 - Endocrine disrupting properties
63 chemicals --> 5 chemicals

Hazardous Chemicals in Plastic Packaging (HCPP) Project

<https://www.foodpackagingforum.org/hcpp-project>

Phthalates are regulated

BBP, DBP, DIBP, DEHP and DCHP uses are regulated including: plasticizers, adhesives, lubricants, binders, coating agents, defoamers, gasket closures, and in materials such as paper, paperboard and plastic.

European Chemical Agency (ECHA)

European Food Safety Authority (EFSA)

US Environmental Protection Agency (US EPA)

US Food and Drug Administration (US FDA)

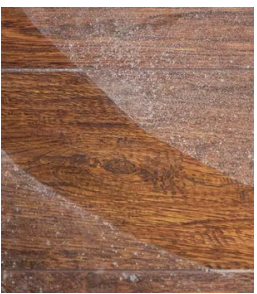
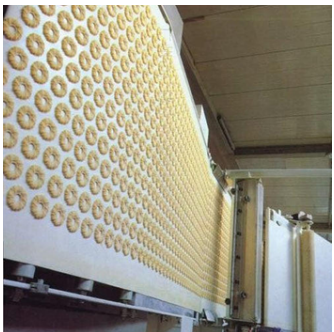
UC Consumer Protection Safety Commission (CPSC)

Regulatory agencies established so-called 'safe' levels: the amount of each chemical above which the risk to human health increases. We referred to them as **Reference dose (RfD)**

Phthalate	Derived from animal studies	RfD ^a Endpoint and effect of concern
DEHP	35	Testicular germ cell depletion and reduced testes weight
DBP	6.7	Reduced spermatocyte development at postnatal day 21, and mammary gland changes in adult male offspring
BBP	500	Reduced anogenital distance and several other endpoints from various studies
DIBP	8.3	Overall potency of DIBP similar to DBP; possible potency difference of 25% between DIBP and DBP

Current ECHA RfD for four phthalates

- Based on animal studies
- The RfDs were based on toxicity to the male reproductive system.
- We didn't find an RfD for DCHP. In the United States, DCHP is not allowed in children toys and children articles at levels above 0.1% (w/w)
- All units are in microgram per kilogram of body weight per day



Phthalates are the
'everywhere' chemicals.
They are part of our
daily life.





**Phthalates have been
in commerce and in
use for more than 60
years**

Are there human data on phthalates' health effects?
If so, what are they and at what levels are observed?

Goal:

To investigate whether regulatory safe levels (RfD) of phthalates are protective of the public of other relevant health outcomes in addition to male reproductive development



What we did

◆ TARGETED LITERATURE SEARCH

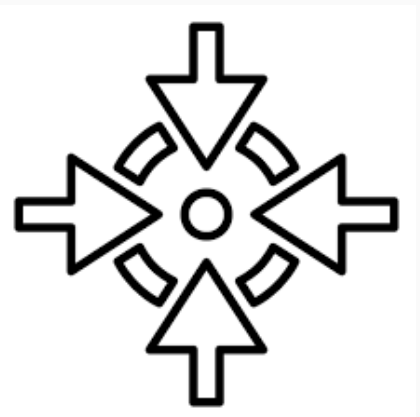
Search terms included chemicals full names, CASRN, synonyms in combination with human exposure+epidemiological studies + metabolites + biomonitoring + children + pregnant women + ...

◆ CRITERIA FOR INCLUSION

Studies must have data on any of the 5 phthalates including 1) **concentration** in any bodily fluid; 2) description of a measured **endpoint**; 3) association between concentration and endpoint must be **statistically significant**

◆ INTAKE ESTIMATION

Identified lowest phthalate concentration statistically significantly associated with and effect and back-calculated the dose or amount of phthalate needed to observe that effect



38 out of 64 publications met our criteria

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

What we found

DEHP, DBP, BBP and DIBP

metabolites showed significant associations with the following endpoints

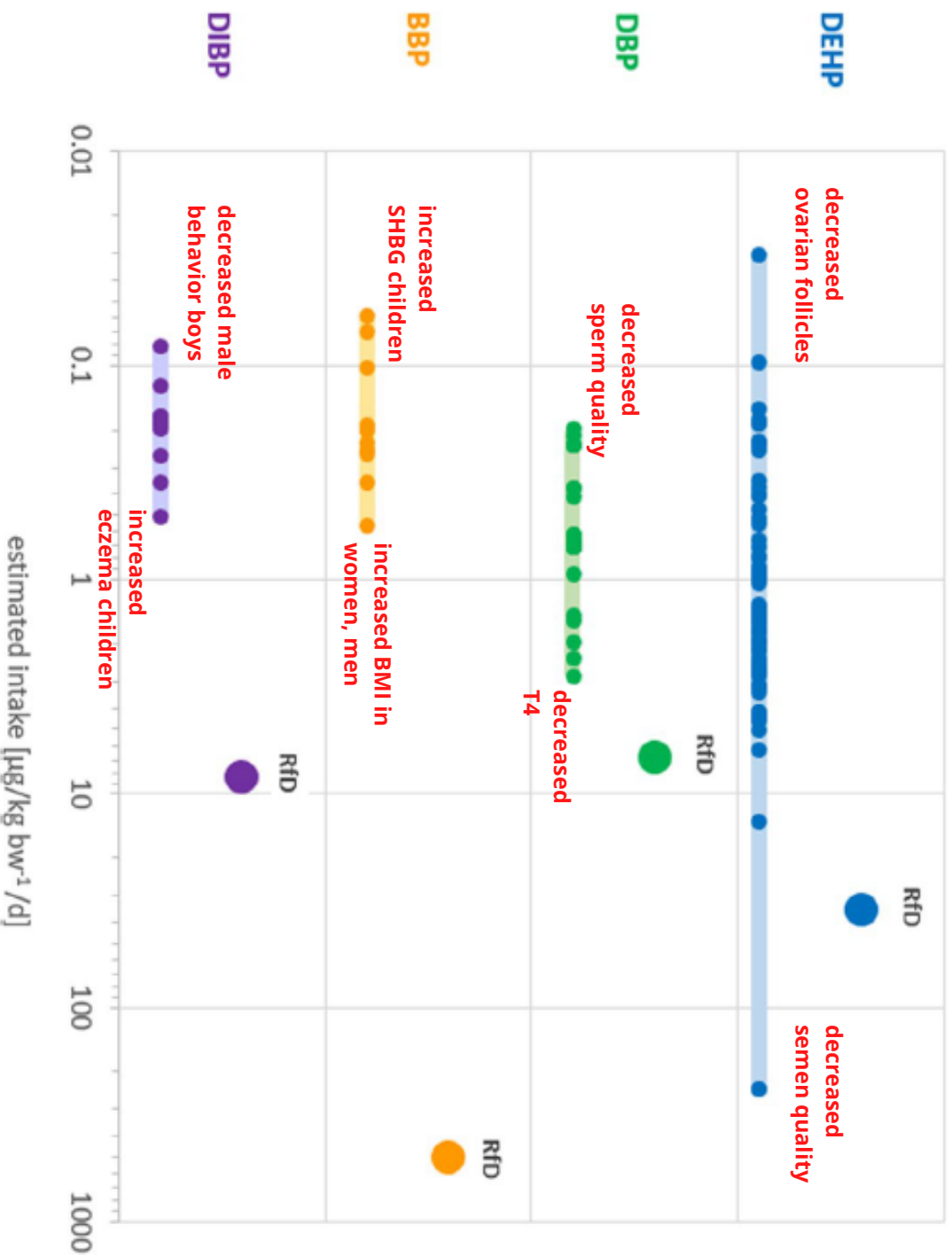
- Reproductive (male and female)
- Neurodevelopmental
- Behavioral
- Hormonal
- Metabolic

What we found

The lowest estimated intakes were associated with effects in women and children

Table 3 Ten lowest estimated intake and significant endpoints by population

Phthalate	Endpoint statistically significant	Effect	Population Tested	Estimated Intake ^a	Reference
DEHP	Number of ovarian antral follicles	Decreased	Women	0.03–0.16 ^b	[39]
BBP	Serum steroid hormone binding globulin in children	Increased	Mothers 3T	0.06	[50]
BBP	Social problems in children	Increased	Mothers 3T	0.07	[64]
DIBP	Masculine play behavior in boys	Decreased	Mothers 2T	0.08	[52]
BBP	Thyroid hormone T3	Decreased	Children (4–9 yo)	0.10	[71]
DIBP	Number of ovarian antral follicles	Decreased	Women	0.13	[39]
DIBP	Motor and psychomotor development in children	Delayed and Decreased	Mothers 3T	0.17	[66]
DEHP	Height standard deviation	Decreased	Children (12 yo)	0.18	[72]
DIBP	Estrogen, testosterone and free testosterone	Decreased	Children (8–14 yo)	0.18	[50, 53]
DEHP	Insulin sensitivity	Increased	Children (12 yo)	0.19	[72]



What we found

For DBP, BBP and DIBP

- Ranges of intake associated with health effects were **below their RfD**

For DEHP

- The highest intake estimate was ~7-times greater than RfD

BBP effects were 8000-5000 times lower than RfD

What we found

Phthalate	Derived from animal studies		Based on human studies			
	RfD ^a	Endpoint and effect of concern	Lowest estimated intake ^a	Significant endpoint	Highest estimated intake ^a	Significant endpoint
DEHP	35	Testicular germ cell depletion and reduced testes weight	0.03	Decreased number of ovarian antral follicles in women [39]	242.5	Decreased semen quality and concentration in men [47]
DBP	6.7	Reduced spermatocyte development at postnatal day 21, and mammary gland changes in adult male offspring	0.19	Decreased sperm motility and semen concentration in men [48]	2.86	Decrease thyroid hormone T4 and freeT4 in women [49]
BBP	500	Reduced anogenital distance and several other endpoints from various studies	0.06	Increased steroid hormone binding globulin in children [50]	0.58	Increased body mass index and waist circumference in men and women [51]
DIBP	8.3	Overall potency of DIBP similar to DBP; possible potency difference of 25% between DIBP and DBP	0.08	Decreased masculine play behavior in boys [52]	0.51	Increased occurrence of eczema in children [53]

^a Units are in microgram per kilogram of body weight per day

DEHP diethylhexyl phthalate; DBP dibutyl phthalate; BBP butylbenzyl phthalate; DIBP diisobutyl phthalate;

Health effects in children

PRENATAL EXPOSURES

- Delayed psychomotor and mental development
- Decreased intellectual, memory and executive development
- Behavioral changes: delinquency, externalization, withdrawn personalities
- Increased odds of ADHD
- Decreased masculine behavior



Metabolic health effects



- Pancreas: insulin resistance (children and adults)
- Thyroid: decrease T4, T3, TSH (children and adults)
- Fat tissue: body mass index, waist circumference, weight

Reproductive health effects

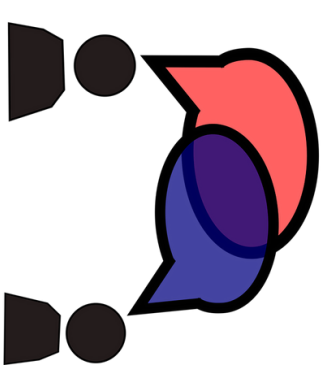


- Reduced number antral follicles
- Decreased number fertilized eggs, total oocytes (low quality)
- Delayed puberty
- Decreased semen quality, sperm count
- Decreased level of male hormones
- Imbalanced hormone levels
- Reduced anogenital distance

Summary and Conclusions

- Epidemiology data show health effects **not commonly assessed in toxicity studies**
- Effects were observed at levels much **lower than current RFD**
- There is substantial **human evidence**
- RfDs are **not bright lines** between no risk/risk; it's more complex
- Scientific knowledge and market behavior are **dynamic**. Safety evaluations must also be
- A **dialogue** between regulators, the medical community, and academic researchers must be established

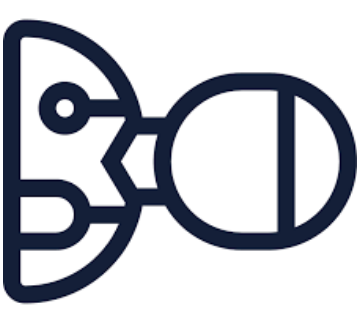
The bookends of environmental health must establish a more fluent dialogue



Regulator



We, the people



Health Practitioner

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

Thambi
Soni!