

American Medical Women's Association



Cancer Prevention and Treatment Fund



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May 31, 2012

**Comments of Patient and Consumer Coalition
on Draft Guidance For Industry
“Limiting the Use of Certain Phthalates as Excipients in CDER-Regulated Products”
[Docket No. FDA-2012-D-0108]**

The above listed members of the Patient, Consumer, and Public Health Coalition appreciate the opportunity to comment on the draft guidance, “Limiting the Use of Certain Phthalates as Excipients in CDER-Regulated Products,” which recommends that industry avoid the use of dibutyl phthalate (DBP) and di(2-ethylhexyl) phthalate (DEHP) as excipients in drug and biologic products.

Although limiting the use of these phthalates is a step in the right direction, the draft guidance should ban the use of DBP and DEHP as excipients because these phthalates have been “shown to be developmental and reproductive toxicants in laboratory animals” and “epidemiological studies suggest certain phthalates may affect reproductive and developmental outcomes” in humans.¹

We are deeply disappointed that the draft guidance would still allow the packaging materials for drugs and biologic products to contain DBP or DEHP, especially since the draft guidance notes that these phthalates can leach from the packaging materials into the drugs, and that “the ubiquitous presence of phthalates in the environment and the potential consequences of human exposure to phthalates have raised concerns, particularly in vulnerable populations such as pregnant women and infants.” Also, setting safety standards for phthalates individually or for individual products without considering their interactions and cumulative effects could underestimate the real-world risks of phthalates in the health of children and adults.

Serious Adverse Effects

Phthalates are called “endocrine disruptors” because they limit or block the body’s natural levels of estrogen, testosterone, and other hormones.

Researchers have shown that, unlike other chemicals, phthalates appear to have more serious effects at *lower* levels than at *higher* levels.² It is often assumed that the higher the dose or exposure, the greater the harm, but endocrine disruptors play by different rules. That is why the director of the National Institute of Environmental Health Sciences, Dr. Linda Birnbaum, says that chemical manufacturers are asking “old questions” when they test for safety even though “science has moved on.”³

In animals, DBP and DEHP have been associated with “the disruption of the development of the male reproductive system.”¹ Research indicates that boys exposed to phthalates may be more likely to develop smaller genitals and incomplete descent of the testicles.⁴ Boys who are born with undescended testicles are 2-8 times more likely to develop testicular cancer later on than men born with both testicles descended).⁵ Additionally, studies by Harvard researchers have shown phthalates may alter human sperm DNA and semen quality.^{6, 7, 8, 9} Phthalates are believed to also affect girls’ hormones, but the impact on breast cancer and other health outcomes are not yet known.

A number of research studies reveal poor health and behavioral outcomes for children exposed to phthalates. For example, there is an association between children’s exposure to phthalates and the risk of asthma, allergies and bronchial obstruction.^{10, 11, 12}

Mount Sinai School of Medicine researchers in 2011 studied the impact of prenatal exposure to “low molecular weight” phthalates—the kind often found in personal care products and the coatings of some medications—on the social behavior of children ages 7 to 9. Children who were exposed to higher levels of these phthalates had worse scores for social learning, communication, and awareness. These children were less able to interpret social cues, use language to communicate, and engage in social interactions.¹³

Columbia University researchers in 2011 discovered that 3-year olds with high prenatal exposure to phthalates were more likely to have motor delays.¹⁴ They also reported that phthalates were linked to certain behavior problems in three-year olds, such as social withdrawal.

Closer Regulation of Phthalates

As noted in the draft guidance, Congress prohibits the use of DBP and DEHP in children's toys; the European Commission prohibits their use as ingredients in cosmetics; the Environmental Protection Agency added them to the list of chemicals of concern; and the Center for Devices and Radiological Health recommends minimizing exposure to PVC devices containing DEHP. It is past time for FDA to issue guidance on the use of phthalates as excipients.

Conclusions

The draft guidance recommends that industry should avoid the use of DBP and DEHP as excipients in drug and biologic products. This recommendation is not strong enough. The FDA should ban the use of DBP and DEHP in excipients especially since "safer alternatives are available."¹ FDA should also ban the use of these phthalates in packaging materials since DBP and DEHP can leach from the packages into the drug and biologic products. Banning DBP and DEHP will help to reduce the "widespread exposure of the general population to phthalates," and reduce the real-world, cumulative negative effects of phthalates in the health of children and adults.¹

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Reproductive Health Technologies Project
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¹ Food and Drug Administration Center for Drug Evaluation and Research (March 2012). Guidance for Industry Limiting the Use of Certain Phthalates as Excipients in CDER-Regulated Products.

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