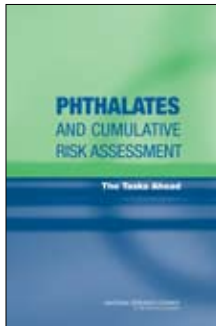


# Phthalates and Cumulative Risk Assessment

## The Tasks Ahead



People are exposed to a variety of chemicals throughout their daily lives. To protect public health, regulators use risk assessments to examine the effects of chemical exposures. This report provides guidance for assessing the risk of phthalates, chemicals found in many consumer products that have been shown to affect the development of the male reproductive system of laboratory animals. Because people are exposed to multiple phthalates and other chemicals that affect male reproductive development, a cumulative risk assessment should be conducted that evaluates the combined effects of exposure to all these chemicals. The report suggests an approach for cumulative risk assessment that can serve as a model for evaluating the health risks of other types of chemicals.

Phthalates are a class of chemicals used in many consumer products to impart flexibility and durability or used for their solvent properties. Concerns have been raised about some phthalates because studies in laboratory animals have shown that exposure can cause adverse health effects, including effects on development of the male reproductive system. Few data are available on the health effects of phthalates in humans, but studies show widespread human exposure to phthalates. The United States and the European Union have passed legislation to restrict the concentrations of several phthalates in children's toys; the European Union has also banned some phthalates from cosmetics.

Given the health concerns about these chemicals, EPA asked the National Research Council to convene a committee to determine whether cumulative risk assessment—an approach that focuses on the health risks posed by multiple chemicals over multiple pathways, routes, and times—of this chemical class should be conducted, and, if so, to identify approaches that could be used for the assessment. However, the committee was not asked to carry out such an assessment in this report.

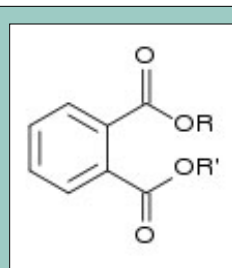
The committee's report concludes that the risks associated with phthalate exposure should be evaluated using a cumulative risk assessment and

provides specific guidance on approaches to that cumulative risk assessment.

The report also considers other chemicals that cause similar effects on male reproductive development, and makes a broader recommendation that the cumulative risk assessment for phthalates should focus on common adverse health outcomes and expand to include these other chemicals. The recommendation to focus on common adverse outcomes represents a shift relative to current practice and is far less restrictive in terms of determining which chemicals to consider for cumulative risk assessments.

### What are Phthalates?

Phthalates, or phthalate esters, are diesters of benzenedicarboxylic acid. This report focuses on the most biologically active phthalates,



The general chemical structure of an *o*-phthalate. R and R' are ester side chains that vary in length and structure. The two side chains can be identical, or they can differ, giving different phthalates different properties.

Common phthalates and examples of their uses.	
Phthalate	Uses
DMP	Insect repellent, plastic
DEP	Shampoo, scents, soap, lotion, cosmetics, industrial solvent, medications
DBP	Adhesives, caulk, cosmetics, industrial solvent, medications
DIBP	Adhesives, caulk, cosmetics, industrial solvent
BBP	Vinyl flooring, adhesives, sealants, industrial solvent
DCHP	Stabilizer in rubber, polymers
DEHP	Soft plastic, including tubing, toys, home products, food containers, food packaging
DOP	Soft plastic

diesters of 1,2-benzenedicarboxylic acid, or *o*-phthalates. Structural differences in the ester side chains of phthalates give them their individual chemical and physical properties and alter their biologic activity.

### Applying Cumulative Risk Assessment to Phthalates

Much can be learned through the traditional risk assessment approach of studying the health effects of exposures to individual chemicals. Such an approach, however, does not reflect the reality of chemical exposures in today's world. Most people are exposed to thousands of chemicals in daily life, and some of these chemicals cause similar health effects. Cumulative risk assessment is an approach that focuses on the combined effects of multiple chemicals.

Two questions were asked to determine whether it would be appropriate to use a cumulative risk assessment rather than a traditional, chemical-by-chemical risk assessment approach for phthalates. First, are people exposed to multiple phthalates? Second, do those exposures contribute to common adverse outcomes? The typical approach to cumulative risk assessment is to focus on grouping chemicals that are structurally similar or are known to have a common mechanism of action, or biological pathway leading to health effects. The report, however, sets out a new vision of cumulative risk assessment representing a departure from that current approach, by proposing to focus instead on chemicals that share common adverse outcomes (see Box 1 for further discussion).

On the basis of the answers to those questions, the report concludes that cumulative risk assessment is the appropriate approach to determining the risks posed by phthalates. In addition, the report recommends that the cumulative risk assessment for phthalates also consider other chemicals that affect develop-

ment of the male reproductive system (known as antiandrogens).

### Exposure to Multiple Phthalates

Phthalates are used in a wide variety of consumer products, including cosmetics, personal-care products, pharmaceuticals, medical devices, children's toys, food packaging, and cleaning and building materials. People may be exposed to phthalates through ingestion, inhalation, absorption through

the skin, or parenteral administration (which occurs with the use of some medical devices).

Although the relative contributions of the exposures to the total body burden at various ages are not known, studies have documented simultaneous exposure to multiple phthalates in the general population, including children and adults. Other studies have shown that phthalates cross the placenta, and multiple phthalates have been measured in animal and human amniotic fluid. After reviewing key studies, the committee concludes that the first question has been affirmatively answered; not only multiple exposures, but multiple exposures at all stages of life, have been demonstrated.

### Common Health Effects of Phthalates

Phthalates have been shown to cause a variety of effects in laboratory animals; however, their adverse effects on development of the reproductive system of male animals have led to particular concern. Those effects include infertility, decreased sperm count, cryptorchidism (undescended testes), hypospadias (malformation of the penis) and other reproductive tract defects and are referred to as the phthalate syndrome. Given these common effects of phthalate exposure that have been observed in laboratory animals, the second question has been answered affirmatively. In addition, the phthalate syndrome in animals has many similarities to a hypothesized syndrome in humans—testicular dysgenesis syndrome—although there are no human data that directly link the hypothesized syndrome in humans with phthalate exposure.

The report emphasizes that not all phthalates are equivalent in the severity of their effect; some phthalates exhibit less severe or no effects. The age at the time of exposure is also critical with respect to the severity of the effects. The fetus is the most sensitive life stage.

## Box 1: A New Approach to Cumulative Risk Assessment

Typically, to determine whether a cumulative risk assessment is warranted, scientists and regulators focus on grouping together chemicals that are structurally similar or are known to have a common mechanism of action—that is, chemicals that affect the body through the same biological pathway. However, that approach often restricts cumulative risk assessment to chemicals that are closely related to each other and ignores the important fact that exposure to different chemicals may result in the same outcomes. Thus, focusing on only the mechanism of action can lead to too narrow an approach. In response, the report recommends that cumulative risk assessment focus on chemicals that cause common adverse outcomes.

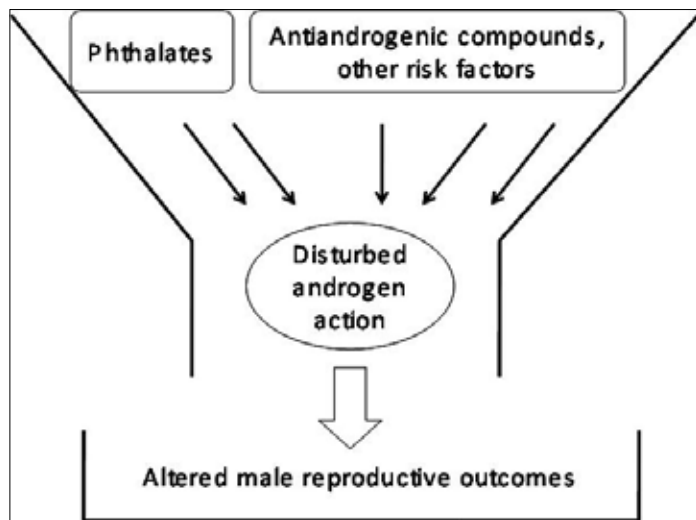
The report acknowledges that moving beyond structural or mechanistic similarity may appear challenging because of the large number of chemicals that might cause common health outcomes and thus warrant cumulative risk assessment. However, the report concludes that such an approach is achievable and would be more directly relevant to the public health goals of EPA and other agencies or organizations by better illuminating the relationships between chemical exposures and human diseases and disorders.

The report maps out how this approach to cumulative risk assessment can be done with phthalates and other antiandrogens. The potential applications of this approach, however, are much broader and could apply to a variety of other chemical exposures. For example, EPA could evaluate combined exposures to lead, methylmercury, and polychlorinated biphenyls, which—although operating through different mechanisms of action—all contribute to cumulative risk of cognitive deficits consistent with IQ reduction in children.

The report emphasizes that the recommendation to focus on common adverse outcomes in cumulative risk assessment does not mean that information on mechanism of action is not important. That information is useful for defining critical pathways, for determining the relevance of effects observed in animals to humans, and for reducing uncertainty in determining risk.

### Health Effects Shared by Phthalates and Other Chemicals

The report concludes that a cumulative risk assessment should be conducted for phthalates and identifies other chemicals that also affect development of the male reproductive system, and therefore should be considered for inclusion in this risk assessment.



Multiple exposures to phthalates and other chemicals can lead to common adverse outcomes; therefore, antiandrogens and other chemicals should be considered for inclusion in a cumulative risk assessment for phthalates.

Phthalates reduce concentrations of testosterone, an important androgen (or male sex hormone) that contributes to the development of male sex organs. This androgen deficiency causes the phthalate syndrome in laboratory animals if it occurs during time periods that are critical for male reproductive development. A number of other chemicals (often referred to as antiandrogens) can cause similar effects, although by different mechanisms or biological pathways, and it is difficult to differentiate between the effects of phthalates and the effects of these other chemicals. Therefore, focusing solely on phthalates to the exclusion of other antiandrogens in assessing risk would be artificial and could seriously underestimate cumulative risk.

### Considerations for Cumulative Risk Assessment for Phthalates and Other Antiandrogens

The report concludes that sufficient data are available to proceed with the cumulative risk assessment of phthalates and other antiandrogens. However, addressing current data gaps would lead to greater refinement of a cumulative risk assessment and reduce uncertainty associated with any risk estimates. The report provides research recommendations and includes the following suggestions:

- Determine prenatal exposure to phthalates at relevant times during pregnancy. Issues surrounding fetal exposure are particularly important because fetal exposure during critical developmental periods have the potential for the greatest effects on development of the male reproductive system.
- Identify the most important sources of phthalate exposure in the general population.
- Identify the full spectrum of phthalate metabolites (which are produced when phthalates enter the body) and identify which metabolites can be used to reliably indicate phthalate exposure.
- Understand the reasons for differences in susceptibility to phthalates based on age, species, and exposure route.
- Explore the potential of phthalates to cause synergisms in combination with other antiandrogens.

The report reviews cumulative risk assessment approaches and outlines a few possible options for a cumulative assessment of phthalates and other antiandrogens, ranging from relatively straightforward to the more complex. Each option will have advantages and disadvantages, and EPA will need to evaluate each and determine which option is most appropriate.

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**Committee on the Health Risks of Phthalates:** **Deborah Cory-Slechta** (*Chair*), University of Rochester School of Medicine and Dentistry; **Edmund Crouch**, Cambridge Environmental Inc.; **Paul Foster**, National Institute of Environmental Health Sciences; **Mary Fox**, Johns Hopkins Bloomberg School of Public Health; **Kevin Gaido**, Hamner Institutes for Health Sciences; **Maida Galvez**, Mount Sinai School of Medicine; **Chris Gennings**, Virginia Commonwealth University; **J. Paul Gilman**, Covanta Energy Corporation; **Russ Hauser**, Harvard School of Public Health; **Andreas Kortenkamp**, University of London School of Pharmacy; **Jeffrey Peters**, Pennsylvania State University; **Donna Vorhees**, The Science Collaborative; **Mary Snow Wolff**, Mount Sinai School of Medicine; **Ellen Mantus** (*Project Director*), **National Research Council**.

The National Academies appointed the above committee of experts to address the specific task requested by the U.S. Environmental Protection Agency. The members volunteered their time for this activity; their report is peer-reviewed and the final product signed off by both the committee members and the National Academies. This report brief was prepared by the National Research Council based on the committee's report.



For more information, contact the Board on Environmental Studies and Toxicology at (202) 334-3060 or visit <http://nationalacademies.org/best>. Copies of *Phthalates and Cumulative Risk Assessment: The Tasks Ahead* are available from the National Academies Press, 500 Fifth Street, NW, Washington, D.C. 20001; (800) 624-6242; [www.nap.edu](http://www.nap.edu).

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