# Aggregate Exposures to Phthalates in Humans

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# A C K N O W L E D G M E N T S

**Contributors**

Joseph DiGangi, PhD, USA,

Ted Schettler MD, MPH, USA

Madeleine Cobbing, UK

Mark Rossi, MA, USA

**Reviewers**

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**Health Care Without Harm**

1755 S St. NW, Suite 6B • Washington, DC 20009 • www.noharm.org • 202-234-0091

# Contents

# Executive Summary

Phthalates are a family of chemicals that are produced in the millions of tons annually worldwide, and are a principal component of many diverse products that consumers come into contact with at home, at work, and in hospitals. They include products made of flexible polyvinyl chloride plastic (PVC), cosmetics and other personal care goods, pesticides, building materials, lubricants, adhesives, and film, among other items. Phthalates are released into the environment by manufacturers and escape from consumer products in which they are used. Worldwide ecosystem contamination and direct contact with phthalate-containing products result in virtually ubiquitous human exposures.

Health effects that may be caused by exposure to phthalates differ among the various individual compounds and depend on the timing and the size of the dose. Young, developing organisms are more vulnerable to exposure to phthalates than adults. In particular, the developing male reproductive tract appears to be the most sensitive endpoint, although effects on the liver, kidneys, lungs, and blood clotting are also of concern. In animal tests considered relevant to humans, several of the phthalates, including di-(2-ethylhexyl) phthalate (DEHP), di-butyl phthalate (DBP), benzyl butyl phthalate (BBP), and perhaps di-isononyl phthalate (DINP), interfere with male reproductive tract development and are toxic to cells in the testes responsible for assuring normal sperm and hormone production.

Human exposure to DEHP from PVC medical devices used in patient care has been known for some time. Expert panels of the US National Toxicology Program (NTP) and Health Canada, as well as the US Food and Drug Administration (FDA), however, have recently reviewed the toxicology of DEHP and considered exposures to patients that may result from the use of DEHP-containing equipment. Each review concluded that some patients are likely to be exposed to potentially unsafe amounts of DEHP while receiving medical care.

Testing by the US Centers for Disease Control and Prevention (CDC) recently showed that phthalate exposures are virtually ubiquitous in the general population. Women of reproductive age experience some of the highest exposure levels to phthalates that can interfere with normal male reproductive tract development.

In this report, we summarize what is known about human exposures to phthalates and consider the potential health impacts of exposure to real-world mixtures of these chemicals. Using a relative potency approach, based on what is known about mechanisms of action and available experimental data, it becomes clear that, for a large number of women of reproductive age, their aggregate exposure to phthalates is sufficient to significantly increase the risk of abnormal development in male fetuses and baby boys. Women of reproductive age who require medical care may be exposed to additional phthalates, largely DEHP, in the medical setting, that, depending on the procedure, can add significantly to their existing levels.

According to sample data from the CDC, an estimated 5% of women of reproductive age from the general population are contaminated with 75% or more of the level of just one of the phthalates, DBP, that may begin to impair normal reproductive tract development in their baby boys. Many of these women are also regularly exposed to significant amounts of BBP and DEHP, so that their aggregate exposures pose even greater risks. When any of these women requires medical care that exposes them to additional DEHP from PVC medical devices, even more is added.

Where are these phthalates coming from in the general population? No one knows for certain, but perhaps the high exposures to DBP in women of reproductive age provide a clue, at least for that phthalate. DBP is used in a variety of cosmetic and personal care products. Recent testing identified DBP in some hair spray, fragrances, and deodorants. Many nail polishes also have large quantities of DBP. Unfortunately, labeling requirements are sufficiently lax so that it is extraordinarily difficult to identify phthalate-containing products and to begin to narrow down the search for the sources of widespread general population exposures.

Chemical policy in the US is severely "Balkanized"[161] and requires major revisions. For example, the Food and Drug Administration is responsible for food contaminants (including phthalates), drug ingredients (including phthalates), medical devices (including phthalate-containing PVC products), and cosmetics (including phthalates). Unfortunately, each of these activities is a responsibility of a different division within FDA, each of which carries out its work in isolation from the others. As a consequence, when the medical device division considers the safety of exposure to DEHP, they consider only medical devices and not the real world of population-wide exposures to multiple phthalates from multiple sources. And, when the cosmetics division considers phthalates in personal care products, not only do they limit their concerns to products in their domain, but they must prove the likelihood of harm with no requirement that manufacturers will supply safety data.

When the Consumer Products Safety Commission (CPSC) considers the safety of phthalates in, for example, children's toys, they consider only the phthalate that may leach out of the toy when a child chews on it, and not the other phthalates that the same child may be exposed to from contaminated food, contaminated air, or medical care.

And when the Environmental Protection Agency (EPA) considers whether or not to allow phthalates in a pesticide formulation, they examine those proposals one at a time, failing to consider aggregate exposures to multiple phthalates from multiple sources.

As a result, phthalates permeate the environment and contaminate large populations of people throughout the world. Phthalates are in the blood of pregnant women at levels of concern, particularly when the contaminants are considered in the aggregate. Phthalates cross the placenta and also contaminate breast milk. Relevant animal tests show that phthalates interfere with normal fetal and infant development.

Manufacturers of phthalates continue to produce large amounts and sell them to product manufacturers who use them in thousands of products. Manufacturers consistently argue that there is no evidence that anyone has been harmed by phthalates. As we note, however, and as confirmed by the NTP panel and FDA, no study has ever examined the impacts of phthalate exposure on the developing male reproductive tract in people. Not one.

Lack of evidence can hardly be used as evidence of safety when no one has ever looked. The increasing incidence of hypospadias, undescended testes, testicular cancer, and declining sperm counts in the US and many other parts of the world suggests that a closer look at many reproductive tract toxicants and endocrine disruptors is urgently needed in people. With respect to phthalates, however, evidence from relevant animal studies and from limited studies of non-reproductive tract impacts in hospitalized patients is sufficient to require phasing out the use of many of the phthalates. As the Health Canada panel concluded, "the status quo is not an acceptable option."

Regulatory agencies charged with protecting medical patients, public health, and the environment must substantially revise procedures and protocols to consider the potential impacts of phthalate exposures in the aggregate, rather than as single chemical exposures. In Europe, vigorous debate is underway regarding the phase-out of the general use of many phthalates in consumer products. Alternatives to phthalates that perform well are currently on the market for nearly every use.

Phthalates also serve as a case-study that demonstrates the failure of current chemical policy in the US. Regulatory authority is spread among agencies that compete with one another rather than cooperate. Lines of communication are limited and infrequently used. No one agency is authorized to look at the "big picture".

Public health and the environment can only be truly protected when safer materials are substituted far upstream in the manufacturing process. Humans have demonstrated the capacity to contaminate every nook and cranny of every ecosystem and every developing fetus with synthetic chemicals that can impair normal development. Now we need to demonstrate that we can change.

First, we need to recognize that a major overhaul of current regulatory policy is long overdue. Under the current framework, government approval simply does not provide adequate real-world protection from chemical exposures. The FDA, the EPA, the CPSC, and other government agencies, with necessary authorization, must begin to transform their make-believe regulatory framework into a new, science-based system that properly considers the reality of aggregate exposures to toxic chemicals and that requires meaningful pre-market testing of commercial chemicals. Second, consumers must insist on the right to know about chemicals in commercial products and must have unhindered access to toxicity and exposure data. Third, manufacturers can and must shift to cleaner production practices and materials that produce cleaner, sustainable products more suited to the contemporary world and the one we will leave to future generations.

# Abbreviations

| | |
|---|---|
| μg | Microgram |
| ATBC | O-acetyl tributyl citrate |
| BEP | Butyl A-ethylhexyl phthalate |
| BBP | Butyl benzyl phthalate |
| CABG | Coronary artery bypass graft |
| CDC | US Centers for Disease Control and Prevention |
| CPB | Cardiopulmonary bypass |
| CPSC | US Consumer Product Safety Commission |
| DBGP | Di-butylglycol phthalate |
| DBP | Di-(n-butyl) phthalate |
| DCHP | Dicyclohexyl phthalate |
| DEHA | Di-(2-ethylhexyl) adipate |
| DEHP | Di-(2-ethylhexyl) phthalate |
| DEHPA | Di-(2-ethylhexyl) phosphate |
| DEP | Diethyl phthalate |
| DHP | Dihexyl phthalate |
| DHP | Di-n-hexyl phthalate |
| DIBE | Di-isobutylhexahydro phthalate |
| DIBP | Di-isobutyl phthalate |
| DIDP | Di-isodecyl phthalate |
| DIHP | Di-isoheptyl phthalate |
| DINP | Di-isononyl phthalate |
| DIOP | Di-isooctyl phthalate |
| DMP | Di-methyl phthalate |
| DOP | Di-n-octyl phthalate |
| DPHP | Di-(2-propylheptyl) phthalate |
| DPOP | Diphenyl 2-ethylhexyl phosphate |
| DPP | Di-n-pentyl phthalate |
| DTDP | Di-tridecyl phthalate |
| ECMO | Extracorporeal membrane oxygenation |
| FDA | US Food and Drug Administration |
| KEMI | Swedish National Chemicals Inspectorate |
| Kg | Kilogram |
| L | Liter |
| L11 | Di-L-undecyl phthalate |
| L7-11 | Di-L-heptyl, undecyl phthalate |
| L7-9 | Di-L-heptyl, nonyl phthalate |
| L9 | Di-L-nonyl phthalate |
| L9-11 | Di-L-nonyl, undecyl phthalate |
| MBP | Mono-n-butyl phthalate |
| MEHP | Mono-(ethylhexyl) phthalate |
| MPP | Monopentyl phthalate |
| NTP | US National Toxicology Program |
| PVC | Polyvinyl chloride plastic |
| RPF | Relative potency factor |
| TETM | Tri-2-ethylhexyl trimellitate |
| TI | Tolerable intake |
| TPN | Total parenteral nutrition |
| UDP | Undecyl dodecyl phthalate |
| US EPA | US Environmental Protection Agency |

# Preface

Health Care Without Harm (HCWH), the campaign for environmentally responsible health care, works to help reduce the public health and environmental impacts of activities associated with medical institutions, without compromising the quality of care. To a large extent, the materials used in medical facilities influence those impacts. Metals, solvents, plastics, pharmaceuticals, radioactive materials, and other toxic compounds can pose threats to public health and the environment, as well as to patients and hospital workers, if they are not carefully chosen and manufactured, used, and disposed of properly.

Polyvinyl chloride (PVC) is one of the predominant plastics used in medical care. Initially, HCWH was concerned with the public health and environmental impacts of the manufacture and disposal of PVC medical products. These concerns centered primarily on the generation of dioxins, furans, and other toxic organochlorine compounds during the manufacture and incineration of PVC. PVC also requires additives to impart certain qualities like stability and flexibility. Medical products made of PVC are usually softened with a plasticizer from the family of chemicals known as phthalates. Under certain circumstances, a considerable amount of the phthalate most commonly used in these devices, di-(2-ethylhexyl) phthalate (DEHP), can leach out of medical devices causing direct patient exposures. A closer look at DEHP leaching led to additional concerns about patient safety. Consequently, HCWH petitioned the US Food and Drug Administration (FDA) to examine the safety of DEHP-containing products more closely. The results of the FDA safety assessment, as well as those of other government-sponsored expert panels are discussed in this report.

HCWH became even more concerned about phthalates when the US Centers for Disease Control and Prevention (CDC) published data about general population exposures. Not only are medical devices only one of a number of sources of phthalate exposures, but the levels of phthalate exposure in the general population are high enough to raise serious questions about their safe use in hundreds of consumer products to which we are regularly exposed. Many people from the general population are contaminated with a significant body burden of phthalates. Some kinds of medical care add more. As these exposures add up, it becomes clear that aggregate phthalate exposures, from multiple sources, raise a significant public health concern.

Where are human exposures to phthalates coming from? We have only partial answers. The search cannot be confined to only one business sector, since phthalates are so widely used in so many products. In addition to medical devices, HCWH looked at information about phthalates in food, air, cosmetics, children's toys, and many other consumer products to help identify other exposure sources. This investigation leads to serious concerns about the adequacy of current regulatory policies and manufacturing practices for protecting public health and the environment. It is a cautionary tale about the risks associated with divided responsibilities and failure to connect the dots.

# Introduction

People and wildlife are regularly exposed to industrial chemicals through food, water, air, or from direct contact with a variety of consumer products. Many of these chemicals are toxic at some dose and under certain conditions of exposure. Attempts to estimate the risks from contact with industrial chemicals rely heavily on understanding their toxicity and the nature of exposures. The route of exposure, whether through ingestion, inhalation, absorption through the skin, or intravenous administration, can significantly influence a chemical's toxicity. The magnitude of exposure is also important, but the timing, duration, and pattern of exposure are also critical factors that determine toxic impacts. We know, for example, that low-level exposures to industrial chemicals that have no discernable effects on adults can have profound and lifelong impacts if the exposure occurs during developmental windows of vulnerability, as, for example, during fetal life, infancy, or childhood.

Chemicals, or their metabolic byproducts with long half-lives, may build up to toxic concentrations in the environment and in people and wildlife. Even those chemicals that do not persist for long periods of time may pose a problem if they are so widely used that we are repeatedly and continuously exposed to them. This report is about such a class of chemicals. They are the phthalates—a family of chemicals that are produced in the millions of tons annually worldwide and used in hundreds of consumer and industrial products. Phthalates are ubiquitous environmental contaminants and are nearly always found at some concentration in virtually all people and wildlife.

This report discusses three parallel lines of research. First, we review the toxicity of members of the phthalate family, with an emphasis on health effects relevant to people. Second, we describe relatively recent data concerning general population exposures to phthalates and consider the sources of those exposures. We discuss those exposures in light of the current understanding of the toxicity of phthalates, and focus our concerns on exposures to women of reproductive age, developing children, and young medical patients. Finally, using studies that shed light on the mechanisms by which phthalates exert their toxicity, particularly with respect to reproduction and development, we conclude that phthalate exposures should be considered in the aggregate when estimating the potential harm that may result from human exposures. Unfortunately, product manufacturers and regulatory agencies responsible for protecting public health and the environment each fail to consider total exposures to this family of chemicals. As a result, a substantial number of people are at risk of harm.

A combination of limited human data and a wealth of animal studies show that phthalates can impair reproduction and development, alter liver and kidney function, damage the heart and lungs, and affect blood clotting. Studies that have focused on cancer as a phthalate-related health concern show that phthalates cause liver cancer in rodents, but many investigators have concluded that the cancer seen in animal tests is not relevant to people because of species differences in response.

Early studies looked largely at impacts in adults, where phthalates seemed to have relatively low acute toxicity. It also seemed that, in adult animals, fairly large doses were necessary to cause impacts on the testes, ovaries, and liver. Scientific reports then showed, however, that some medical patients exposed to DEHP, a phthalate that leaches from PVC, or polyvinyl chloride plastic medical devices, receive doses that are similar to those causing health effects in laboratory animals.

Reports in the scientific literature over the past 10-15 years have raised additional concerns. Developing organisms are uniquely vulnerable to phthalate exposures, and, in particular, the developing male reproductive tract appears to be the most sensitive organ system. Abnormal development of the testes, penis,

and other components of the male reproductive tract occurs at levels of exposure that are hundreds or thousands of times lower than those necessary to cause damage in adults. Several expert panels, including those assembled by the US Food and Drug Administration (FDA), the National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction (NTP), and Health Canada (HC) have recently independently concluded that those animal studies are relevant for predicting health impacts in people.

The second line of research addresses human exposures to phthalates. One of the phthalates, di-(2-ethylhexyl) phthalate (DEHP) is added to polyvinyl chloride (PVC) plastic to soften and make flexible this inherently rigid material. DEHP-containing PVC is used for many purposes, and one application is in a variety of medical products. Under certain circumstances, depending on the product and the purpose for which it is used, DEHP leaches out of these devices causing direct patient exposures. The FDA, NTP, and HC have each determined that the level of exposure can, in some instances, rise to a level of serious concern, particularly in vulnerable individuals, such as fetuses and infants, and even in adults who are repeatedly exposed.

Beyond health care institutions, however, the CDC studied phthalate exposures in the general population. The results were surprising. Virtually all people studied had some level of various phthalate by-products in their urine, indicating widespread exposures. But some people had far higher concentrations than others. When the investigators looked more closely at highly exposed subgroups, they found that women of reproductive age were among them. This is a particularly troubling finding, in light of the particular vulnerability of the fetus to phthalate toxicity.

A third line of research has examined the mechanisms of phthalate toxicity and considered the cumulative or aggregate impacts of members of the phthalate family in experimental animals. Studies show that some industrial chemicals act as anti-androgens, interfering with male development in at least two ways. They can decrease testosterone synthesis in the fetal testes or they can block the androgen receptor through which testosterone initiates its control over male development. In either case, testosterone-dependent gene activation is reduced. Several phthalates interfere with testosterone synthesis in the developing organism, including DEHP, BBP, DBP, and perhaps DINP.[6 63 107 109] It follows that exposures to these phthalates should be considered in the aggregate for the purposes of estimating risks from exposure. Moreover, exposure to these phthalates should be considered in the aggregate with exposures to other chemicals that are also anti-androgenic through androgen receptor blockade or interference with testosterone synthesis.

The problem is that regulatory agencies generally do not estimate risks from chemical exposure by considering aggregate exposures. They assess safety as if we are exposed to single chemicals, despite real world evidence of multiple exposures to multiple chemicals from multiple sources. There are two notable exceptions. The EPA has been directed by Congressional legislation to consider cumulative exposures to pesticides used on food when the chemicals act through a common mechanism of action. The other is in the pharmaceutical division of the FDA where there is some recognition that biologically active drugs often interact with each other and may have additive effects. Physicians, nurses, and pharmacists are routinely expected to consider drug interactions and cumulative impacts when prescribing, administering, or providing medications. Most patients also understand this concern and have learned to ask about it when new medications are considered.

In the medical products division of the FDA, however, their 2001 Safety Assessment of DEHP Released from PVC Medical Devices compares an estimated safe exposure level (tolerable intake) to individual kinds of therapy. They acknowledge that patients are exposed to DEHP from multiple medical sources, but focus their safety analysis on single sources. The FDA safety assessment also concentrates entirely on sources of phthalate exposure in the medical care setting and fails to consider exposures to phthalates in individuals from the general population who also happen to require medical care. Data from the CDC show that pregnant women come to the hospital already significantly contaminated with phthalates, and medical exposures add more. And, when the FDA assesses the safety of phthalates used in cosmetics, they typically consider only exposures to one kind of phthalate from individual cosmetic products. No regulatory agency is adding up all the exposures to all of the phthalates from all of the sources and assessing the safety of that real world mixture. Yet, many people in the general population are currently exposed to various phthalates at levels of concern.

In this report we outline an approach that attempts to address the reality of multiple sources of phthalate

exposures. We know far less than we ought to about the consequences of exposure to real world complex mixtures of industrial chemicals. For the phthalates, however, available exposure and toxicity data make it clear that the world in which people and wildlife live is not the make-believe world of the FDA, the EPA, and the Consumer Product Safety Commission. People are exposed to phthalates at levels of significant concern. As we will see, however, people are not being protected by product manufacturers or regulatory agencies, and are hard-pressed to find ways to protect themselves.

# Phthalates in Consumer Products

Phthalates are a principal component of flexible PVC products, cosmetics, pesticides, building maintenance products, lubricants, and personal care goods that surround consumers at home, work, and in hospitals. PVC without additives is inherently a rigid and brittle material, requiring large amounts of plasticizers to make flexible products. In fact, approximately 90% of global plasticizer production is destined for use in polyvinyl chloride plastic (PVC). [14] The remaining 10% is used in adhesives, caulks, skin creams, detergents, electrical capacitors, hairsprays, inks, solvents, lubricating oils, lotions, nail polish, paints, fragrances, and pharmaceuticals.[23 74 120] In personal care products, phthalates provide flexibility, impart an oily "moisturizing" film, and help dissolve and fix other cosmetic ingredients. [15] The film forming and flexibility properties imparted by phthalates are also useful in paints, inks, fillers, adhesives and caulks and insulating properties in electrical cabling and capacitors. [25]

## Phthalate structure

The oily, plasticizing properties of phthalates come from their chemical structures. Phthalates represent a broad chemical family containing a benzene ring, two carbonyl groups, and two alcohol groups to generate a diester structure. Common branched phthalates such as DEHP, DBP, BBP, and DINP feature branched-chain alcohol moieties of 6 to 13 carbons. The linear phthalates contain linear alcohol groups and include short chain phthalates such as DEP and DMP, and other phthalates with chain lengths of seven to 11 carbons that are use to impart increased flexibility at low temperatures. [48] The benzene ring-based structure of phthalates helps reduce their viscosity but also makes them harder to degrade. [68]

Phthalates move freely through the PVC polymer to impart flexibility and other characteristics.[144] Since they are not covalently bound to the polymer, they are fairly easily released to air, water, saliva, blood, IV solutions, nutritional formulas, and other extracting materials. [46 86 110 153] Since phthalates tend to be fat soluble, they leach more readily into lipid-containing solutions. Depending on the circumstances of use, 2% - 50% of the phthalate content can emerge from products over their service life. [86]

## Phthalates in personal care and other consumer products

Many personal care products, building materials, clothing, toys, adhesives, inks, pesticides, films, food wraps, food containers, and other consumer items contain phthalates. Phthalate concentrations in personal care products can approach and sometimes exceed 200 gm/kg (20%). [5] Other consumer products can contain levels of phthalates ranging from 60 - 800 gm/kg (6-80%). [36 86 116 141] Four of the principal phthalates used in commerce are BBP, DBP, DEHP, and DINP. Butyl benzyl phthalate (BBP) is added to cosmetic products, flooring, paints, coatings, adhesives, and printing inks. [45 113] Di-n-butyl phthalate (DBP) is used in cosmetics, toys, flooring, adhesives, wallpaper, furniture, raincoats, plastic cling wrap, and shower curtains. [1 4] Di-(2-ethylhexyl) phthalate (DEHP) is the principal phthalate used in a variety of products including medical devices, cabling, flooring, and auto parts and interiors. [86] Di-isononyl phthalate (DINP) is widely used in children's toys, flooring, fabrics, gloves, tarps, garden hoses, shoes, autos, paper packaging materials used for food contact, and sealing gaskets for food containers. [24 114] See Table 1 for examples of phthalates in commerce.

A recent study by the Danish EPA tested PVC shower curtains, flooring, gloves, carpet tiles, wallpaper, and bags and found at least one type of phthalate in all products at levels that varied from 24 - 630 gm/kg.[30] Combined levels of DIDP-DINP were found at 88 gm/kg in shower curtains, 110 gm/kg in bags, 260 gm/kg in wallpaper, 290 gm/kg in carpet tiles, 310 gm/kg in flooring, and 600 gm/kg in gloves. A recent Greenpeace study found phthalates at levels up to 390 gm/kg in a variety of PVC consumer products made for children including diaper pants (DINP), diaper-changing mats (DINP), rain covers for strollers (DEHP), drinking straws (DINP), crib-rail teethers (DINP), and hats (DEHP).[67]

## Phthalates in PVC medical products

PVC medical products also contain phthalates. Levels of DEHP, the most commonly used, range from 200-800 gm/kg (20-80%).[36 116] PVC products that release DEHP in the clinical setting include IV storage bags, ventilator tubing, IV infusion sets, endotracheal tubes, IV infusion catheters, nasogastric tubes, blood storage bags, enteral and parenteral nutrition storage bags and tubing, blood administration sets, urinary catheters, exam gloves, suction catheters, chest tubes, nasal cannula tubing, hemodialysis tubing, syringes, extracorporeal membrane oxygenation (ECMO), and cardiopulmonary bypass (CPB) tubing.[153]

**Table 1. Types of products containing phthalates**

| Product Type | Examples | Phthalates |
|---|---|---|
| Automotive | PVC auto floor mats | DEHP |
| | Auto sheeting | L11 |
| | PVC underbody | DINP |
| | PVC upholstery | DEHP |
| Beauty | Aftershaves | DEP |
| | Deodorants | DBP, DEP |
| | Skin Creams | DEP |
| | Hair preparations | BBP, DMP, DBP, DEP |
| | Nail polishes | DBP |
| | Fragrances | DEHP, BBP, DBP, DEP |
| | Powders | DEP |
| Building -Home | Adhesives | BBP, DHP, DIOP, DIDP |
| | PVC carpet covers | DEHP |
| | Caulks /grouting | unspecified |
| | Paint | unspecified |
| | PVC drawer liners | DEHP, DINP |
| | PVC flooring | BBP, DEHP, DBP |
| | PVC furniture covers | DEHP |
| | PVC garden hoses | DIBP |
| | PVC gaskets | BBP, DEHP, DINP, L7-9, L7-11 |
| | PVC inflatable furniture | DEHP |
| | PVC inflatable pools | DEHP |
| | PVC insulation | DEHP |
| | PVC mattress pads | DEHP |
| | PVC roofing film | DEHP |
| | PVC shades | DEHP, DINP |
| | PVC shower curtains | DEHP, DBP |
| | PVC tarps | DEHP |
| | PVC tubing | BBP, DEHP, DINP, L7-11 |
| | PVC wall coverings | L7-9, DINP, DEHP, DBP |
| | PVC water beds | DEHP |
| | PVC-coated fabrics | L7-9 |
| | PVC-covered cables | DEHP, DIDP, L11, L7-11 |

**Table 1. Types of products containing phthalates (continued)**

| Product Type | Examples | Phthalates |
|---|---|---|
| Consumer | PVC aprons | DEHP |
| | PVC backpacks | DEHP |
| | PVC balls | DEHP |
| | PVC bibs | DEHP |
| | PVC changing pads | DEHP |
| | PVC clothing | DEHP, DINP |
| | PVC crib rail teether | DINP |
| | PVC diaper pants | DEHP |
| | PVC luggage | DEHP, DBP |
| | PVC notebook covers | DEHP |
| | PVC packaging | DEHP |
| | PVC purses | DEHP |
| | PVC shoes | DIBP, DEHP, DINP |
| | PVC stroller covers | DEHP |
| | PVC tablecloths | DEHP |
| | PVC toys | DEHP, DINP |
| | PVC umbrellas | DEHP |
| | PVC weight covers | DEHP |
| Food Packaging | PVC squeeze bottles | unspecified |
| | PVC packaging | unspecified |
| | PVC straws | DINP, DEHP |
| | PVC tubing | unspecified |
| | Cling Wrap | unspecified |
| Industrial/Agriculture | Electric capacitors | DEHP |
| | Fillers | unspecified |
| | Pesticides | DEHP |
| | Printing ink | BBP, DBP |
| | PVC conveyer belts | DINP, L7-11 |
| | Vacuum pump oil | DEHP |
| Medical | PVC blood bags | DEHP |
| | PVC catheters | DEHP |
| | PVC colostomy bags | DEHP |
| | PVC dentures | DBP |
| | PVC enteral feeding bags | DEHP |
| | PVC gloves | DEHP |
| | PVC IV bags | DEHP |
| | PVC mattress covers | DEHP |
| | PVC oxygen tents | DEHP |
| | PVC pillow case covers | DEHP |
| | PVC syringes | DEHP |
| | PVC tubing | DEHP |
| | PVC urine bags | DEHP |
| Pharmaceutical | Coating ingredient | DBP |
| | Stabilizer | DBP |

**Sources:** [4 5 24 49 74 86 98 114 127 144]
See the Health Care Without Harm website for updates to this table: **http://www.noharm.org**

## Lack of consumer notification

This widespread use of phthalates in consumer products is largely invisible to the public because most products do not require labels to identify their presence. PVC building products, PVC toys, PVC auto parts, PVC clothing, PVC baby products and other common PVC consumer products do not require labeling that reveals their phthalate content or even identifies the plastic as PVC. The US Food and Drug Administration (FDA) requires some labeling of cosmetic ingredients, but the law does not require listing of phthalates or other ingredients considered fragrance components nor does the law require labeling of products sold to professional salons.[152]

According to a voluntary reporting system used by the FDA, DEP-containing products include 42 colognes, 7 powders, 8 aftershaves and 8 skin creams.[151] The Agency also lists DMP in 11 hair preparations and DBP in 120 nail basecoats, polishes and enamels and 27 other manicuring preparations. Since this is a voluntary system and manufacturers have no obligation to report, a comprehensive analysis of the use of phthalates in personal care products is not publicly available.

Labeling requirements on medical products vary considerably, and the agency does not require manufacturers to note the presence of PVC or phthalates specifically. Some products warn against the use of DEHP-containing IV bags to administer certain drugs that can accelerate DEHP leaching.[76 77] The FDA is currently drafting a risk management strategy as a follow up to their September, 2001 safety assessment of DEHP in PVC medical devices. That strategy may include labeling recommendations.

## Phthalates in the environment

The manufacture, use, and disposal of PVC and other phthalate-containing products have resulted in extensive environmental releases of phthalates. Consequently, phthalates are now one of the most abundant industrial pollutants in the environment, and are widely present in air, water, soils, and sediments. [29 140]

Available data underestimate the release of phthalates from manufacturing facilities since companies are not required to report releases of many commonly produced chemicals. In the US, for example, companies are not currently required to report releases of DINP, DEP, or BBP, despite their high production volume. However, large US industries are required to report environmental releases of DBP and DEHP to the US EPA as part of the Toxic Release Inventory when annual releases exceed 25,000 pounds or when the facility otherwise uses in excess of 10,000 pounds.[32] In 1999, the top 100 US companies reported total DBP releases of more than 390,000 pounds. The same year, the top US 100 companies emitting DEHP reported nearly 1.2 million pounds of releases. In Germany, total DEHP emissions during processing were estimated at over 1.5 million pounds per year in 1998 and the overall annual environmental releases of DEHP in Germany are estimated to be considerably in excess of 3.3 million pounds. These reports, however, do not include phthalates released to the environment from the use or disposal of finished consumer products.

Phthalates such as DEHP have been measured in virtually all fresh water and marine environments and in lake sediments, storm water runoff, sewage treatment plants, and sewage sludge. DEHP, DBP, and DEP were found at levels exceeding 700 $\mu$g/kg in sediments from Lake Mead, a national park in the US.[13] DEHP is in ocean sediments at sewage outfall points (25 mg/kg) and all the sediments in rivers near sewage outflows in New Jersey, USA.[3] DEHP is also the most prominent toxic organic chemical in sewage sludge.[57] DEHP levels in sludge have been measured at 55 – 300 mg/kg. More than five billion pounds of sludge are spread onto US land each year. [3]

Buried PVC products in landfills release phthalates into landfill leachates. [31] DEHP levels in these liquids have been measured at 34-7,900 $\mu$g/kg.[3] In the US, DEHP, DEP, and DBP have been found in 18%, 44%, and 30% respectively, of the hazardous waste sites designated as national priorities for clean-up (Superfund sites.) [3 4 5] In Sweden, Italy, Germany and the UK, various phthalates and their metabolites have also been detected in landfill leachates. Phthalate concentrations for phthalic acid, DEP, and DMP were 18,900 $\mu$g/kg, 540 $\mu$g/kg, and 300 $\mu$g/kg respectively. [9]

DEHP has been measured in indoor air at concentrations ranging from 8 ng/cm$^3$ to 3 mg/cm$^3$. [99 156] A Health Canada Expert Panel evaluation of the risks associated with DEHP exposures concluded that inhalation exposure to DEHP is second only to ingestion of DEHP-contaminated food. [35] Presumably DEHP air contamination is the result of its being released from PVC in the indoor environment.

Even remote areas contain phthalates. DEHP has been found in the Antarctic pack ice, the Antarctic sub-surface snow at depths up to three meters, and in deep-sea jellyfish from more than 3000 feet below the surface of the Atlantic Ocean. [3 100]

## Phthalates in people

Given the multiple uses of phthalates in hundreds of consumer products and worldwide environmental contamination with phthalates, it comes as no surprise that people and wildlife are virtually universally exposed to phthalates. The general population is exposed to phthalates through food, water, air, and the use of phthalate-containing consumer products that may be eaten, inhaled, or applied directly to the skin and absorbed. Whatever the sources, most people are regularly exposed to phthalates so that some combination of these chemicals or their byproducts can be detected in the blood or urine of virtually everyone in the general population.

Unlike some chemicals, like dioxin, lead, or mercury, that tend to persist and build up in various tissues, phthalates are generally not persistent, though under some circumstances, phthalates do tend to accumulate in certain organs.[80] But because exposures are so frequent and common, some level or body burden of the phthalate family of chemicals can regularly be detected. The potential health impacts of these universal exposures are discussed in the following sections of this report with special attention paid to groups of people who are disproportionately exposed.

# Phthalate Toxicity

Phthalates display a variety of toxic effects in animal studies following chronic exposure or even after short-term exposures in particularly vulnerable organisms. These effects include damage to the liver, kidney, heart, and lungs as well as adverse effects on reproduction, development, and blood clotting. The effects of human exposures to phthalates have not been well studied. Long latency periods between relevant exposures and health impacts, unquantified exposures, and subtle effects that are difficult to detect complicate and limit the few existing epidemiological studies of phthalate impacts in humans. But these limitations do not fully explain why the impacts of phthalates on humans have not been thoroughly investigated.

The testicular toxicity of DEHP in experimental animals, for example, was described in 1972, but no one has investigated its effect on human male reproductive capacity.[10 116] Even the consequences of potentially high exposures to DEHP from, for example, total parenteral nutrition or hemodialysis of breastfeeding mothers have not been the subject of scientific review. Although most toxicity data come from studies in laboratory animals, human correlates to some effects seen in animal studies have also been described. This body of data collectively has generated concern in the medical and public health communities as well as government regulatory agencies.

## Reproductive and developmental effects

In general, the monoester metabolite of the parent phthalate compound is thought to be responsible for adverse reproductive and developmental effects of phthalates. In animal testing, impacts include decreased fertility in females, fetal defects, reduced survival of offspring, birth defects, altered hormone levels, and uterine damage. Phthalates that display one or more of these effects include BBP[39 40 41 44 64 109 121], DBP[40 92 131], DEP[52 92], DHP[92], DIDP[75 155], DINP[64 114 150], MBP[38 130], MDP[43], and MEHP[97 129].

In males, phthalates cause prostate damage, female-like areolas/nipples, and reproductive malformations in infants, including altered hormone levels, testicular atrophy, reduced sperm production and motility, undescended testes, hypospadias, Sertoli cell damage, and Leydig cell tumors. Phthalates that display one or more of these effects include BBP[2 64 109 121 134], DBP[42 54 56 106 108 157], DEHP[8 12 56 64 65 94 124], DEP[19 82 92], DHP[92], DINP[64 114 150], DPP[55], MEHP[71], MBP[71], and MPP[71].

Some of the effects caused by DEHP in males include altered zinc concentrations, testicular atrophy and infertility.[153] The FDA notes that these same symptoms are seen in male hemodialysis patients. In fact, the Agency called the similarity between the testicular damage observed in animals and male hemodialysis patients "strikingly similar" and concluded that the effects seen in rodents "may have a clinical correlate in humans."[153]

Several other government agencies have concluded that the reproductive effects caused by DEHP are relevant to humans. The US NTP's Center for the Evaluation of Risks to Human Reproduction (CERHR) Expert Panel concluded in its review of DEHP toxicity that the "rodent data are assumed relevant to predicting that DEHP has the potential to produce adverse reproductive system effects in

humans."[116] In 2001, the Swedish National Chemicals Inspectorate concluded in its review of DEHP for the EU that, "The effects on testis, fertility, and development, observed in different animal species and at relatively low levels, are considered to be relevant to humans."[86] Finally, in 2002, Health Canada's Expert Advisory Panel on DEHP in Medical Devices concluded that, "the mechanism by which developmental and testicular toxicity in particular occur in rodents appears relevant to humans."[69]

## Altered liver and kidney function

Phthalates such as DBP, DEHP, and DINP cause a variety of alterations in kidney function in animals including renal cysts, reduction in creatinine clearance, and transitional cell carcinoma.[20 27 158]

Phthalates also increase liver weight, affect liver function, and alter liver enzymes in rodents. These effects have been observed after exposure to DBP, DEHP, DMP, DEP, DINP, and DIDP.[4 17 52 87 133 150] Some, but not all, of the liver changes seen in rodents are thought by many researchers not to be relevant to humans (see below). However, certain effects due to phthalate exposure have been observed in both primates and humans. In a small study of monkeys, for example, DEHP caused adverse effects in the liver after leaching from PVC blood bags during blood transfusions.[79] In contrast, transfusions given to two monkeys from polyethylene containers without DEHP did not cause liver damage. Human patients undergoing hemodialysis are also exposed to large doses of DEHP from PVC tubing. Changes in liver enzymes similar to those observed in animal studies are also seen in these patients.[153] In the US alone, approximately 250,000 people require dialysis treatment.[111]

Other human liver effects that have been reported to occur following DEHP exposure include cholestasis, in which bile excretion is impaired. One prospective study found cholestasis in infants undergoing extracorporeal membrane oxygenation (ECMO).[135] These infants received large doses of DEHP, which leached from PVC tubing. Another study failed to find ECMO-related cholestasis when exposure to DEHP was lower.[83] Cholestasis and other liver abnormalities are also observed in neonatal infants receiving total parenteral nutrition.[59] The cause(s) of these liver abnormalities are not fully understood, and the potential role of DEHP has never been fully investigated. The high lipid content of the nutrition solution facilitates phthalate leaching from DEHP-containing products, and these patients likely receive even larger DEHP doses than dialysis patients.[96] A recent Health Canada Expert Advisory Panel recommended that "total parenteral nutrition solutions be administered to newborns and infants only via products which do not contain DEHP."[69]

DEHP and DINP cause liver carcinoma and adenomas in rodents.[20 89 105] These tumors are linked to the proliferation of small cellular organelles known as peroxisomes. In humans, peroxisome proliferation in the liver after exposure to phthalates and other peroxisome proliferators is generally not found to an appreciable degree. Therefore, one possibility is that phthalates do not have the potential to cause liver cancer in humans. However, phthalates cause peroxisome proliferation by interacting with a nuclear steroid hormone receptor that governs gene expression. This receptor is also found in humans but at 1-10% of the amount observed in rodents.[86] Since the difference between the human and rodent receptor is quantitative, the potential for human response may vary with the receptor content in different individuals. In fact, a 10-fold difference in receptor transcription has been observed in different individuals.[146] These observations led a researcher in the field to conclude that, "the potential human carcinogenicity of these chemicals cannot be summarily ignored."[154]

## Heart, lung, and hematologic effects

Phthalates can also adversely impact the heart and blood pressure, though many animal studies have used fairly high exposure levels. One study, however, using intravenous injection of MEHP in rats, reported a slowing of the heart rate beginning at a total dose of 57 mg/kg and a drop in blood pressure beginning at 157 mg/kg.[126] Patients undergoing coronary artery bypass grafting can be exposed to 2.2-80 mg MEHP/operation and patients undergoing heart transplants 0.5-2.5 mg/operation.[11] Neonates undergoing exchange transfusion can be exposed to MEHP at levels up to 0.68 mg/kg.[138] Little is known about species differences in susceptibility to cardiac effects of phthalates.

The effects of phthalates on the lung are not well known. DIDP increases the width of alveolar septa and causes inflammatory reactions in animal studies.[60] In humans, lung disorders similar to hyaline

membrane disease occurred in several pre-term infants ventilated with PVC tubing containing DEHP.[128] The symptoms diminished when the PVC tubing was replaced with ethylene vinyl acetate tubing that does not contain plasticizers. A 1999 study found that phthalates such as DEHP and BBP migrate from PVC flooring to house dust.[117] The authors reported a higher frequency of children with bronchial obstruction, characteristic of asthma attacks, in homes with PVC flooring.[78] They proposed that the structural similarity between phthalates and prostaglandins might provide a mechanistic explanation for the observed association.

The FDA cites numerous studies that indicate that DEHP stimulates complement activation and platelet aggregation and that these effects are significantly reduced when non-PVC/non-DEHP alternatives are used.[153] According to the FDA, complement activation appears to be involved in the inflammatory response observed in cardiopulmonary bypass patients. Platelet aggregation can lead to the formation of small blood clots that are thought to cause neurological complications in cardiopulmonary bypass patients and infarcts of the brain, lung, and kidney in patients that receive extracorporeal membrane oxygenation.[53]

## Potential role of isomeric mixtures in phthalate toxicity

Phthalate toxicity can be further complicated by the presence of large numbers of isomers or chemical variants. In a study of DINP, the US Consumer Product Safety Commission (CPSC) noted that DINP is a mixture of up to 100 isomers and that only five have been even minimally studied.[149] One type of DINP was carcinogenic, but the CPSC claimed that it was never commercialized. However, the agency did warn that, "It is conceivable that one or more existing types of DINP for which data are unavailable could also be more toxic and/or carcinogenic."[149]

# Exposures Resulting from Medical Procedures

The deposition of DEHP in human tissues resulting from the use of DEHP-containing PVC medical products has been documented for thirty years. In 1972, DEHP released from PVC blood-bags was detected in the lungs, liver, spleen, and abdominal fat.[80] In the mid-1970s, investigators found significant levels of DEHP in the heart and gastrointestinal tract of neonatal infants treated with PVC umbilical catheters.[72] Higher levels of DEHP were correlated with more extensive transfusion, catheter use, and death. In 1976, DEHP was found in human serum following hemodialysis.[62 93] In 1985, DEHP and its more toxic metabolite, MEHP, were found in hemodialysis patients.[123] Both the parent compound and its metabolite were also found in newborn infants who had received exchange transfusions.[137 138] Sjoberg et al., (1985) measured post-exchange transfusion levels of MEHP in plasma of newborn infants at 2.4-15.1 $\mu$g/mL. In 1989, DEHP was also found in the blood, liver, heart, and testes of neonatal infants undergoing extracorporeal membrane oxygenation.[132] Ventilation with PVC tubing also deposits DEHP in the lungs.[128] In the 1990s, further evidence accumulated of DEHP deposition due to exchange transfusions and dialysis and its high exposure potential from infusion lines used in total parenteral nutrition.[50 96 122]

## FDA Safety Assessment of DEHP

In 2001, the FDA released its Safety Assessment of DEHP Released from PVC Medical Devices.[153] The Agency estimated DEHP exposures from a variety of medical procedures and compared the results to their calculated tolerable intake for DEHP. Table 2 shows that a variety of medical procedures result in DEHP exposures close to the tolerable intake established by the Agency. These procedures include IV infusion with drugs requiring pharmaceutical vehicles for solubilization, adult total parenteral nutrition, adult coronary artery bypass graft (CABG) replacement transfusion, neonatal replacement transfusion, adult orthotopic heart transplant, and adult hemodialysis. In addition, the FDA estimates indicate that several procedures exceed the Agency's tolerable intake of DEHP. These include total parenteral nutrition with lipids in neonates, transfusions to trauma patients and ECMO in adults, neonatal exchange transfusions, adult coronary artery bypass graft, adult and neonatal artificial heart transplant, and adult and neonatal enteral nutrition.

The FDA concluded that DEHP exposures may not be safe for patients receiving medical treatments that exceed the tolerable intake as shown in Table 2. The Agency also expressed concern over the risk to children and cited three main findings:

1) Children receive a greater DEHP dose than adults from some procedures;
2) Metabolic differences may cause children to absorb more DEHP, create more of its toxic metabolite, MEHP, and excrete less MEHP; and
3) Children may be more sensitive to the toxic effects of DEHP than adults.

The FDA safety assessment of DEHP is consistent with the conclusions of the National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction. In 2000, the NTP Expert Panel concluded in its review of DEHP that:

> "The available reproductive and developmental toxicity data and the limited but suggestive human exposure data indicate that exposures of intensively-treated infants/children can approach toxic doses in rodents, which causes the Panel serious concern that exposure may adversely affect male reproductive tract development."[116]

## Table 2. Estimated DEHP doses from PVC medical products for various medical procedures calculated by the US FDA compared to tolerable intakes (mg/kg/day)

| Procedure | DEHP Dose | Tolerable Intake | Ratio Tolerable Intake/Dose* |
|---|---|---|---|
| IV infusion | | | |
| Crystalloid solutions | 0.005 | 0.6 | 120 |
| Drugs requiring solubilization | 0.15 | 0.6 | 4 |
| TPN | | | |
| Adult; added lipid | 0.13 | 0.6 | 5 |
| Neonatal; added lipid | 2.5 | 0.6 | 0.2 |
| Transfusion | | | |
| Adult; trauma patient | 8.5 | 0.6 | 0.1 |
| Adult; ECMO | 3.0 | 0.6 | 0.2 |
| Adult; CABG replacement | 0.28 | 0.6 | 2 |
| Neonate; exchange | 22.6 | 0.6 | 0.02 |
| Neonate; replacement | 0.3 | 0.6 | 2 |
| Cardiopulmonary bypass | | | |
| Adult; CABG | 1.0 | 0.6 | 0.6 |
| Adult; orthotopic heart transplant | 0.3 | 0.6 | 2 |
| Adult; artificial heart transplant | 2.4 | 0.6 | 0.3 |
| ECMO | | | |
| Neonate | 14 | 0.6 | 0.04 |
| Dialysis | | | |
| Adult hemodialysis | 0.36 | 0.6 | 2 |
| Adult peritoneal dialysis | <0.01 | 0.6 | >60 |
| Enteral nutrition | | | |
| Adult | 0.14 | 0.04 | 0.3 |
| Neonate | 0.14 | 0.04 | 0.3 |

**Data source:** [153]
**Abbreviations:** IV: intravenous; TPN: total parenteral nutrition; ECMO: extracorporeal membrane oxygenation; CABG: coronary artery bypass graft. See the Health Care Without Harm website for updates to this table: **http://www.noharm.org**
*a ratio of <1 means that the dose exceeds the tolerable intake

# Limits of the FDA Safety Assessment

The FDA failed to consider two significant issues when comparing the tolerable intake for DEHP to exposures from various medical procedures:

1) Although the agency mentioned the problem of aggregate exposures to DEHP from multiple medical sources, they did not take this reality into account when listing medical procedures that might result in exposures in excess of the tolerable intake.
2) When calculating the tolerable intake for DEHP, the FDA attempted to factor in exposures to other phthalates in the hospital setting. But, they failed to consider exposures to all phthalates in the general population that result in a pre-existing body burden in patients entering the health care system.

## Aggregate exposures in the hospital

DEHP is not the only phthalate to which patients are exposed in the hospital. The FDA cites studies that identified DBP, DEP, DMP, or BEP in PVC medical devices including nasogastric tubing, microfilters, butterfly catheters, denture base material, infusion tubing, infusion bags, and intestinal tubing. Levels of these additional phthalates varied from 1% to 20% in the medical products.[153]

The FDA derived a tolerable intake for DEHP, which included a safety factor of 3 that is intended to account for both "increased sensitivity to DEHP-induced testicular effects during pre- and post-natal exposure and the possibility that humans can be exposed to phthalates other than DEHP and MEHP that exert their effect via a similar mechanism of action." Based on relevant animal studies, an increased sensitivity to DEHP-induced testicular effects in very young developing organisms seems clear. Whether or not a safety factor of 3 is sufficient protection for that population is a matter of conjecture. Beyond that, however, the Agency limited their consideration of concurrent exposures to multiple phthalates to those resulting only from medical care. If one considers concurrent exposure to multiple phthalates from multiple sources, including those that result in a body burden of phthalates before a patient enters a medical facility, a different picture emerges. A safety factor of 3, intended to account for both increased prenatal/postnatal sensitivity and multiple phthalate exposures from all sources, appears to be inadequate.

In addition, the FDA notes that, in some instances, DEHP metabolizes to its toxic metabolite MEHP prior to the initiation of medical therapies. This transformation is facilitated by lipases present in stored blood and plasma, but can also occur by hydrolysis in stored IV solutions. The FDA cites studies that measured MEHP in hospital patients undergoing coronary bypass, hemodialysis, and peritoneal dialysis. The Agency also acknowledged that nursing infants could receive significant doses of MEHP in breast milk from mothers undergoing hemodialysis. The FDA performed some calculations to estimate the impact of MEHP that are described further in Appendix I. However, in the end, the Agency focused only on DEHP when listing procedures that might result in exposures exceeding the tolerable intake.

In conclusion, although the FDA acknowledges that individual patients can be exposed to DEHP from multiple sources in the medical setting and to multiple phthalates from medical devices, they fail to integrate that information into the real world in which patients live—a world where people are exposed to multiple phthalates from non-medical and medical sources at levels that, for many prospective patients, are close to or exceed FDA's tolerable intake.

# Aggregate Exposures in the General Population

Human exposure to phthalates in the general population has been recognized for over 30 years, but the levels of contemporary exposures were demonstrated in a study recently conducted by the US Centers for Disease Control and Prevention (CDC). The results suggest that some of the highest exposures to phthalates occur in women of childbearing age, a population that is most vulnerable to phthalates' ability to damage the developing child. Previous attempts to measure phthalates in human tissue have been complicated by their ubiquitous presence that contaminates samples and prevents accurate measurement. A new analytical method developed by the CDC permitted estimates of phthalate exposure by determining levels of their monoester metabolites in urine.

## The CDC study

In 1999, investigators from the CDC measured the levels of various chemicals in blood and urine samples from 1,029 people, six years or older, as part of the National Health and Nutrition Examination Survey (NHANES).[23] Among the chemicals of interest were seven common phthalates. Investigators measured metabolites of these phthalate parent compounds in urine samples of the participants. The study revealed evidence of population-wide exposures to multiple phthalates with DEP, DBP, and BBP present at the highest levels. Breakdown metabolites of DEHP, DOP, and DINP were also observed. Surprisingly, the concentrations of DEP, DBP, and BBP metabolites exceeded those of DEHP and DINP, even though DEHP and DINP are produced in larger volumes and are more widely used. This may reflect lower exposures, storage in fat or other tissues, or metabolism and excretion by a different pathway.[15]

The results of this study suggest that we know far less than we should about the sources of human exposure to these industrial chemicals produced in high volume and used for so many different purposes. Perhaps the extensive use of both DEP and DBP in cosmetic products, including perfumes, nail polishes, lotions, deodorants, and hairsprays, which result in skin absorption or inhalation, explains the CDC findings. Or perhaps other combinations of consumer products are also responsible. We don't know.

### A closer review of an important subset

CDC scientists examined a subset of the initial population more closely. This sub-group consisted of 289 participants who were 20 – 60 years old. Fifty-six percent were females and the group included Caucasians (39%), African-Americans (30%), and Mexican-Americans (23%). The study measured breakdown metabolites of DEP, DEHP, DBP, DCHP, BBP, DOP, and DINP in random urine samples.[15] Phthalate exposures were higher and more common than in the larger study population. More than 75% of the participants excreted metabolites of DEHP, DEP, BBP, and DBP. An analysis of demographic factors revealed the study's most disturbing finding. The highest levels of the DBP monoester (MBP) were found in women of childbearing age. In fact, six of the eight highest MBP levels for the entire 289-member group were found in women of reproductive age.

Given what is known about the pharmacokinetics of these chemicals, scientists from the CDC and the National Institute of Environmental Health Sciences (NIEHS) back-calculated to estimate the oral intake of individual phthalates that would be expected to result in the observed urinary residues.[90] The calculations were applied to the 289-person sub-group and a steady-state intake and clearance was assumed. The 289 participants were further divided into two demographic groups:

1) women of reproductive age between 20 and 40 years old (n=97) and
2) the rest of the adult sample (n=192).

The authors considered their estimates to be within an order of magnitude of the true value due to limited understanding of absorption, transformation, and excretion and its high variability.

## Exceeding previous intake estimates

Estimates of exposure to phthalates in the two demographic groups, based on actual measurements of urinary metabolic residues, exceeded previous daily intake estimates, which had been based largely on contaminated food intake, for almost all of the phthalates. Table 3 shows exposure estimates for the two groups. In this sample, women of reproductive age are exposed to BBP, DBP, and DEP at levels that are 2 – 45 times higher than previous daily intake estimates. The rest of the adult group shows BBP, DBP, and DEP exposures that are 1.7 – 30 times higher than previous daily intake measurements for adults. In the 95th percentile and above, women of reproductive age are exposed to significantly higher levels of DBP than the population at large (32 vs. 6.5 μg/kg/day). That is, in this study, the upper 5% of the population of women of reproductive age are estimated to have oral-equivalent intakes of DBP of 32 μg DBP/kg/day or higher while the upper 5% of the rest of the population is estimated to have oral-equivalent intakes of 6.5 μg DBP/kg/day or higher.

## Demographic differences in phthalate exposures

Using the NHANES data, CDC and NIEHS scientists also examined other demographic differences in phthalate exposures.[91] They determined that individuals with a high school education or less had higher levels of DBP than those with an education beyond high school. Lower income and lower educational level was associated with higher levels of BBP exposure. DEHP exposures were higher in males, in urban populations, and in lower income individuals.

CDC scientists also examined exposure to phthalates in children using the same methods as prior studies with adults.[18] The study group contained 14 boys and 5 girls between 12 and 18 months old. The children live in an agricultural area of California, USA. Metabolites of BBP, DBP, and DEP were detected in all 19 children. Six children also contained the breakdown product of DEHP. Median exposure levels in these children were approximately the same as adult exposures for DBP and BBP, and somewhat lower for DEP. For MEHP, the median values were approximately the same, though the number of children was small.

A recent study of 46 African-American women 35-49 years old from the Washington DC area reported levels of urinary metabolites of several phthalates and compared them to results from the CDC NHANES study. The median level of MEHP (the metabolite of DEHP) in the African-American women was more than twice as high as adults in the

**Table 3. Estimated phthalate exposures in the 95th percentile group of women of reproductive age and general population compared to previous estimates of daily intake. (μg/kg/day)[90]**

| Phthalate | Women of reproductive age (95th percentile) | Rest of group (95th percentile) | Daily Intake Estimate (μg/kg/day) |
|---|---|---|---|
| All phthalates | | | 1-11 UK |
| DEP | 90 | 130 | 4.0 US |
| DBP | 32 | 6.5 | 1.9 Canada |
| BBP | 4.5 | 3.4 | 2.0 Canada |
| DCHP | 0.24 | 0.25 | |
| DEHP | 3.8 | 3.5 | 3.8 - 30 US<br>5.8 Canada<br>12 EU |
| DOP | 0.65 | 1.0 | <3.0 US |
| DINP | 3.7 | 1.4 | <3.0 US |

References for daily intake estimates for adults: all phthalates: UK[103], EU (multiple pathway) [86], DEP: [5], BBP: [46], DBP: [22], DEHP: US [3], DEHP: Canada [21], DINP: [114] and DOP: [115].

**Table 4. Estimated exposures in women of reproductive age compared to regulatory limits for phthalates. (μg/kg/day)**

| Phthalate | CSTEE Tolerable intake | US EPA Reference Dose | Women of Reproductive Age (95th percentile) |
|---|---|---|---|
| DEP | | 800 | 90 |
| DBP | 100 | 100 | 32 |
| BBP | 850 | 200 | 4.5 |
| DCP | | | 0.24 |
| DEHP | 50 | 22 | 3.8 |
| DOP | 370 | | 0.65 |
| DINP | 150 | | 3.7 |

**Abbreviations:** CSTEE: EU Scientific Committee on Toxicity, Ecotoxicity and the Environment; EPA: Environmental Protection Agency. Exposure data from the CDC.[90] CSTEE Tolerable Intake values[46] from EPA Reference Doses available at **http://www.epa.gov/iris/index.html.** See the Health Care Without Harm website for updates to this table: **http://www.noharm.org**

NHANES study (6.4 vs. 2.8 μg/gm creatinine), and about twice as high for MBP (the metabolite of DBP; 43.4 vs. 22 μg/gm creatinine).[73] MEP levels were approximately the same.

## Individual adult exposures and regulatory limits

The CDC calculations of phthalate exposures demonstrate surprisingly high levels of phthalates in the bodies of women during their childbearing years. However, the regulatory systems in the US and European Union view each phthalate exposure individually instead of collectively. Table 4 compares the exposure for each phthalate to its regulatory limit. The data show that none of the phthalate exposures exceeds exposure limits. In fact, phthalate manufacturers use this data to conclude that exposures to phthalates are negligible.[33]

## Assessing aggregate exposures to multiple phthalates: a relative potency approach

Actual human exposures to chemicals do not occur singly, but in aggregate, complex mixtures. In addition, many phthalates display similar toxic effects as a group.[64] These realities require a new approach to assessing phthalate exposures and impacts that result from exposure to multiple phthalates in mixtures from multiple sources in order to protect public health.

In 1996, the Food Quality Protection Act directed the US EPA to consider aggregate exposures to pesticides for chemicals that exert their toxicity through a common mechanism of action. Since then, the FDA and the Swedish National Chemicals Inspectorate (KEMI), have also acknowledged the importance of considering aggregate phthalate exposures.[85 153]

Estimating the relative potency of individual chemicals and adding them in order to estimate the total potency of a mixture is one way to evaluate the impacts associated with aggregate exposures. Two pieces of information are useful for justifying this approach. First, it is helpful to know something about mechanisms of action. A relative potency approach is justified when chemicals exert their toxicity, at least in part, through a common mechanism of action or a final common pathway. Second, a common endpoint or related set of endpoints adds to the evidence that chemicals may have at least additive effects in an organism.

For the phthalates BBP, DEHP, DBP, and perhaps for DINP, this approach is supported by the general consensus that these phthalates act, at least in part, through a common mechanism when they independently cause harmful effects on the developing male reproductive system, which appears to be their most sensitive endpoint. DEHP, BBP, and DBP each reduce testosterone synthesis in the developing male organism.[6 63 107 109] It should also be noted that antiandrogens that act by blocking the androgen receptor will also likely have a cumulative impact with chemicals that interfere with testosterone synthesis. Each mechanism will reduce the effective level of activated androgen receptors at the level of the gene—the final common pathway of toxicity.

For phthalates, the potency of each component in a mixture can be expressed relative to DEHP, the most well characterized member of the phthalate family. Each individual phthalate can then be converted to a "DEHP-equivalent" for the purpose of estimating the total potency of a mixture of different phthalates. This approach is similar to using "toxic equivalency factors" for estimating the toxicity of complex mixtures of other chemicals, like, for example, dioxins, that also act through a common mechanism of action. The DEHP-equivalent potency of the mixture can then be calculated by adding the DEHP-equivalency of each individual phthalate. This approach requires data that directly compares endpoint-specific toxicity of various individual phthalates with DEHP. These calculations assume that the combined effect of a mixture is additive, though it is certainly possible for a combination to be more toxic than the sum of its individual parts.

## Relative potency calculations

We applied the relative potency approach to phthalates shown to cause reproductive and developmental toxicity in males. Few data are available that compare these toxic effects from exposures to various phthalates in the same experiment. However, two well-controlled studies did compare other phthalates with DEHP for this endpoint in vivo.[64 65] To determine the relative potency, the ability of each phthalate to cause a certain effect was compared with DEHP. For example, two litters of rats exposed prenatally and through lactation to equal amounts of DEHP or BBP showed different results. For DEHP, 87% of the infant males displayed female-like areolas/nipples after exposure, but for BBP 70% of the males displayed this defect.[64] This suggests that BBP is roughly 80% as effective as DEHP at causing this effect, and therefore, could be assigned a relative potency value of 0.8.

Another recent rodent study compared the impacts of gestational exposures to DEHP, DBP, or DEHP + DBP on the developing male reproductive tract. Pregnant rats were given DEHP (100 mg/kg/day), DBP (100 mg/kg/day), DEHP + DBP (each at 100 mg/kg/day) on gestational days 12-21 by gavage. DBP and DEHP + DBP caused similar reductions in anogenital distance in male offspring when compared to controls, but DEHP at that dose caused no reduction in anogenital distance. The doses chosen, therefore, were too low to detect potential additivity, since DEHP alone at that dose had no effect. With respect to male areolae/nipple retention, an additive response from DEHP + DBP was observed at postnatal day 13, though it did not achieve statistical significance, perhaps as a result of the dose and the small number of animals in each dose group.[163]

### Relative potencies of several phthalates

Table 5 shows the potencies of four phthalates relative to DEHP. The relative potency of BBP varied from 1.0 to 0.8 for effects including development of female-like areolas/nipples, reduced pup weight, shortened anogenital distance, malformed males, and reduced testis weights. DBP showed greater variability in its effects compared to DEHP. Hypospadias was the only effect in which DEHP was much more potent. Estimating the relative potencies for DBP is complicated by the fact that DBP was used at lower doses than DEHP. We ignore this dosing difference, however, for the purposes of estimating their relative potency, and still note that DBP is similar to DEHP in potency for shortened anogenital distance. For other effects, potency ranged from 0.5 – 0.6 that of DEHP. DINP showed much less potency than DEHP in producing malformed males, but about 0.3 the potency for generating female-like areolas/nipples. DEP did not produce either malformed males or male infants with female-like areolas/nipples in these experiments. In other studies, DEP increased testes weights, altered Leydig cell structure, and decreased sperm concentration.[19 82 92] However, these studies did not directly compare DEP to DEHP.

To calculate exposure in a mixture of phthalates, a relative potency value must be selected for a phtha-

## Table 5. Estimated potencies of phthalates relative to DEHP: Reproductive and developmental toxicity in males.

| Effect | Phthalate | Dose (mg/kg) | Percent of animals or size of impact | Relative Potency | Study |
|---|---|---|---|---|---|
| Male infants with female-like areolas/nipples | DEHP | 750 | 87 | 1.0 | [64] |
| | BBP | 750 | 70 | 0.8 | |
| | DINP | 750 | 22 | 0.3 | |
| | DEP | 750 | 0 | 0 | |
| Reduced pup weight at birth | DEHP | 750 | 15 | 1.0 | |
| | BBP | 750 | 18 | 1.0 | |
| Malformed males | DEHP | 750 | 82 | 1.0 | |
| | BBP | 750 | 84 | 1.0 | |
| | DINP | 750 | 7.7 | 0.1 | |
| | DEP | 750 | 0 | 0 | |
| Reduced testis weights | DEHP | 750 | 35 | 1.0 | |
| | BBP | 750 | 35 | 1.0 | |
| Shortened anogenital distance | DEHP | 750 | 30 | 1.0 | |
| | BBP | 750 | 30 | 1.0 | |
| | DEHP | 750 | 2.45 | 1.0 | [65] |
| | DBP | 500 | 2.79 | 1.1 | |
| Percent areolas At birth in male infants | DEHP | 750 | 88 | 1.0 | |
| | DBP | 500 | 55 | 0.6 | |
| Hypospadias | DEHP | 750 | 67 | 1.0 | |
| | DBP | 500 | 6.2 | 0.1 | |
| Testicular and epididymal atrophy or agenesis | DEHP | 750 | 90 | 1.0 | |
| | DBP | 500 | 46 | 0.5 | |

All phthalates dosed orally. Note that no corrections were made to the effects in experiments where different doses of DEHP and DBP were used. See the Health Care Without Harm website for updates to this table: **http://www.noharm.org**

late. However, Table 5 shows a variety of relative potencies for each phthalate. Since a higher relative potency value means a higher total estimated effective exposure, the highest relative potencies were selected for each phthalate for the purposes of the calculations in this paper. This conservative rationale yields relative potencies for BBP, DBP, DINP, and DEP of 1.0, 0.9, 0.3, and 0 respectively.

Relative potency factors determined for BBP, DBP, DINP and DEP were applied to the phthalate exposures calculated by the CDC for women of reproductive age and other adults. A sample calculation is shown in Table 6. The exposure level of each phthalate is multiplied by the relative potency to yield the DEHP-equivalent dose. Unfortunately, relative potency factors could not be calculated for DCP and DOP, two phthalates that were measured in the CDC study, because of lack of experimental data.

Total phthalate exposures are likely to be higher than estimates derived from this list since several common phthalates are not included. These high-production chemicals include DHP, DIDP, and DOP as well as a host of new linear chain phthalates.

**Table 6. Using relative potency values to calculate the DEHP-equivalent dose individual phthalates in women of reproductive age in the CDC study**

| Phthalate | Women of reproductive age 95th percentile/max (μg/kg/day) | Relative potency potency | DEHP-equivalent (μg/kg/day) |
|---|---|---|---|
| DEP | 90 (95%)<br>170 (max) | 0 | 0 |
| DBP | 32<br>113 | 0.9 | 29 |
| BBP | 4.5<br>7.8 | 1.0 | 4.5 |
| DCP | 0.24<br>0.45 | | |
| DEHP | 3.8<br>10 | 1.0 | 3.8 |
| DOP | 0.65<br>1.5 | | |
| DINP | 3.7<br>7.8 | 0.3 | 0.9 |

Exposure data from the CDC.[90] Relative potency values calculated above. The DEHP-equivalent dose is the product of the exposure and the relative potency. The total DEHP-equivalent dose is the sum of the individual doses.

## Exceeding tolerable intakes

DEHP-equivalent exposures from the CDC data were calculated and compared to some current tolerable intakes. Clearly, in this sample population, DBP is the individual phthalate with the highest estimated exposure and the one that tends to drive aggregate exposures, expressed as DEHP-equivalents, most sharply toward the tolerable intake. As seen in Table 7, 5% of women of reproductive age from the general population in the CDC study show evidence of exposure to just DBP, expressed as DEHP-equivalency, that is 75% of the FDA's oral tolerable intake. This is without any consideration of exposure to additional phthalates with toxic impacts that are additive to those of DBP. If, for example, one of these women were to be exposed to DEHP from a medical procedure, 25% or less of FDA's calculated tolerable intake would be necessary before her aggregate exposure would exceed safe levels. Women from the general population who happen to be in the top 5% of exposure for DEHP, BBP, and DBP will exceed the tolerable intake without any additional exposure from medical care. Total maximum exposure to just DBP, BBP, and DEHP, based on these estimates, would be on the order of 130 μg/kg/day. Assuming that DBP, BBP, and DEHP are roughly equivalent in potency for impacts on male reproductive development, that daily exposure to these three phthalates would exceed the DEHP tolerable intake by 3 fold.

One study describes the co-variability of exposure to several of these phthalates, or the extent to which exposures to one correlates with exposures to another.[91] In the NHANES sample population, DBP exposure was highly correlated with BBP exposure and BBP exposure was moderately correlated with DEHP. This suggests that there may be common exposure sources for some phthalates, and that women with high DBP levels are also likely to have higher levels of BBP.

**Table 7. Calculated daily intake of individual phthalates from the CDC study referenced to DEHP and compared to regulatory levels for DEHP. (μg/kg/day) for the most highly exposed women of reproductive age in the general population**

| Group Women of reproductive age-top 5% | Total DEHP-equivalent dose | EPA Reference Dose (DEHP) | FDA TDI Oral (DEHP) | Health Canada TDI (DEHP) | CSTEE TDI (DEHP) |
|---|---|---|---|---|---|
| DBP | 29 or higher | 22 | 40 | 44 | 50 |
| BBP | 4.5 or higher | 22 | 40 | 44 | 50 |
| DEHP | 3.8 or higher | 22 | 40 | 44 | 50 |
| DINP | 0.9 or higher | 22 | 40 | 44 | 50 |

**Abbreviations:** TDI: tolerable daily intake; EPA: US Environmental Protection Agency; FDA: US Food and Drug Administration; CSTEE: Science Committee of Toxicity, Ecotoxicity and the Environment for the European Union. The mixture contained DEHP, DBP, BBP, DINP, and DEP. Note that the table only reflects a DEHP-equivalent dose for the male reproductive toxicity endpoint. DCP and DOP could not be included due to the lack of comparative experimental data. See the Health Care Without Harm website for updates to this table:**http://www.noharm.org**

## Limits of the relative potency approach

The aggregate exposure calculations shown above highlight some of the limitations of the relative potency approach. For example, the lack of comparison data for DEP in Table 6 resulted in a relative potency factor of 0 even though the compound shows reproductive effects in other studies.[19 82 92] The lack of comparison data limits the utility of this approach when a large number of phthalates are at issue because it may underestimate total potency of a mixture. In addition, a low relative potency for one endpoint may be unrelated to a relative potency calculated for a different endpoint. Although it would be useful to use No-Observable-Adverse-Effect-Levels (NOAEL) for comparison purposes, those dose estimations have not been determined for many of these impacts on the developing male reproductive system, and the calculations were based on single-dose studies. Finally, value judgments are used to assign an actual relative potency number to a chemical that will be used to determine equivalent doses. The wide variation in relative potencies observed in Table 5 can demonstrate close to a one-to-one equivalence or a one-to-ten equivalence for the same phthalate.

### A significant exposure problem

The relative potency calculations suggest that aggregate exposures to phthalates in the general population are, in many cases, near to, or above regulatory levels for the developing male reproductive toxicity endpoint. Assuming that the population sample studied by the CDC is representative of the total US population, census data reveal the public health implications of the data.

If the CDC sample is representative of the general US population, approximately 2 million women of reproductive age would be exposed to just DBP on a daily basis at levels, expressed as DEHP-equivalents, that are 75% or more of the tolerable intake for DEHP. DEHP, BBP, DINP, and other phthalates add to this number. An unknown number of these 2 million women who happen to be pregnant run the risk of being exposed to unsafe levels of DEHP, if they require medical care provided from DEHP-containing medical devices, even if the DEHP exposures are well below the FDA's tolerable intake. These women will not have been free of phthalates before medical care is provided. On the contrary, as we have seen, baseline exposures in the general population are significant and set the stage for potentially unsafe levels of exposure to phthalates from any number of sources.

These exposure estimates are disturbing even if only in utero male developmental toxicity is considered. The wider spectrum of health effects caused by phthalates adds additional concern to the widespread exposures in the general population.

## Table 8. US Census 2000 data and National Center for Health Statistics calculations of samples in the CDC study

| To Calculate | Category | Number |
|---|---|---|
| Women in upper 95th percentile | Adults 20-44 | 104,004,252 |
| | Women 20-44 | 52,938,164 |
| | Women 20-44 95th percentile | 2,646,908 |
| Children born to women in upper 95th percentile | Births to women 20 to 40 in 2001 | 3,579,886 |
| | Births to women in 95th percentile or above | 178,994 |
| | Male births to women in 95th percentile or above | 89,497 |

US Census 2000 data from **http://www.census.gov**. Birth data from the National Vital Statistics Report at **http://www.cdc.gov/nchs/**. Note that the CDC sample of reproductive age women was between 20 and 40, not 44 as provided in Census data. An approximate estimate of this category would be 2 million for reproductive age women.

# A Legacy of Inadequate Responses

Phthalates have become ubiquitous environmental and human contaminants. The concern over their potential impacts on human health expressed by the FDA, NTP, Health Canada, and the EU Scientific Committees and the CDC's documentation of aggregate exposures in humans reinforces the need to seriously examine and learn from the legacy of industry and government policies surrounding their use.

## Inadequate industry solutions

The chemical industry has dealt with regulatory pressures on phthalates by proposing voluntary agreements and switching to alternative plasticizers. In 1986, DEHP in chew toys came under scrutiny in the US. Toy makers responded by entering into a voluntary agreement with the US Consumer Product Safety Commission to substitute DINP for DEHP.[7] In 1998, toy makers assured the public and US regulators that the voluntary agreement had successfully removed DEHP from children's toys in 1986. However, toys containing DEHP were found the same year at national chain stores in the US.[37 145] Currently, the $70 billion European PVC industry is actively lobbying the European Commission for a voluntary approach to regulating PVC in the EU.[125]

Voluntary agreements fail to ensure safety because compliance is optional and usually unsupervised by the industry, regulators, or outside groups. When industry voluntarily proposes to solve one phthalate problem by switching to another phthalate or plasticizer, the substitution decision can be weighted toward solutions that are easier for the industry rather than safer for consumers. Changing to different plasticizers is relatively easy for manufacturers since alternative phthalates or other plasticizers of PVC can often be produced in the same facilities. Since voluntary agreements allow companies to market consumer products with substitute plasticizers, leaching and exposure problems remain with new concerns about the safety of the substitutes.

Plasticizer leaching problems can be avoided by switching to materials that are inherently flexible, requiring no plasticizers to impart flexibility.

Recent controversies surrounding PVC and phthalates in toys and medical products have led to the substitution of alternative plasticizers. The chemical industry estimates that there are approximately 50-100 plasticizers in commercial use.[47] Common non-phthalate plasticizers in flexible PVC include adipates (e.g., DEHA), citrates (e.g., ATBC), phosphates (e.g., DEHPA), and trimellitates (e.g., TETM). Most are poorly characterized toxicologically, but a summary of some known properties from a Danish EPA report is shown in Table 9.[28] Non-phthalate plasticizers can also leach from PVC causing exposures, though the degree of leaching may vary from that of phthalates.[26] In addition, alternative plasticizers may share some of the liver, reproductive, and developmental toxicity features of phthalates. The No-Observable-Adverse-Effect-Levels (NOAEL) for reproductive toxicity of these common alternative plasticizers varies from 28 – 100 mg/kg/day compared with a 3.7 – 2,800 mg/kg/day for DEHP.[28 153]

## Inadequate government solutions

Government approaches to phthalate regulation have not protected consumers and hospital patients from aggregate phthalate exposures. A patchwork of governmental policies and regulations usually considers only individual chemicals and individual products. No regulatory agency is adding up the multiple phthalate exposures from multiple sources in order to draw safety conclusions.

Regulatory authority is dispersed both among governmental agencies and within agencies and is separated by product category, such as consumer products, pesticides, medical devices, pharmaceuticals, food, and cosmetics. This separation creates formidable barriers

## Table 9. Properties of some alternative plasticizers

| Plasticizer | Properties | Current/Potential PVC Use | Effects |
|---|---|---|---|
| DEHA | Easily migrates | Cling wrap, medical products, packaging | Negative effects on liver, kidney, spleen, and fetus<br>Liver adenomas and carcinomas<br>Skeletal and ureter defects<br>Toxic to crustaceans<br>NOAEL: fetal toxicity 28 mg/kg/day |
| ATBC | Water soluble<br>Expected to be bioaccumulative | Toys, medical products, packaging | Decreased blood pressure and respiration<br>Central nervous system toxicity<br>Decreased body weights in male offspring<br>NOAEL: reproductive toxicity 100 mg/kg/day |
| DEHPA | Water soluble | Medical products, cabling, flooring, wall coverings, packaging | Increased liver weights<br>Causes weakness, irritability, headache, second-degree skin burns, and eye irritation in humans<br>Harmful to algae, crustaceans, fish<br>NOAEL: insufficient data |
| TETM | Heat resistant<br>Easily migrates<br>Expected to be bioaccumulative | Medical products, packaging, cables, floor and wall coverings | Skin and eye irritation<br>Increased liver and spleen weights<br>LOAEL: liver and spleen 42 mg/kg/day |

**Source:** [28] **Abbreviations:** NOAEL: No-Observable-Adverse-Effect-Level; LOAEL: Lowest-Observable-Adverse-Effect-Level. See the Health Care Without Harm website for updates to this table: **http://www.noharm.org**

to regulatory control of aggregate exposures to toxic chemicals of all sorts from multiple sources. A phthalate prohibited or limited for one use can be present in high concentrations in another product. For example, the allowable concentration of DEHP is limited in food containers but not in medical devices. In light of the multiple applications of phthalates in a wide variety of products, focusing on only one product or class of products is unlikely to have a substantive impact on total population-wide exposures.

Regulatory authority is also limited. For example, the Federal Food, Drug, and Cosmetics Act (FDCA) authorizes the FDA to regulate food, drugs, medical devices, and cosmetics. The Agency can deny the marketing of cosmetics that contain "a poisonous or deleterious substance which may render it injurious to health."[51] However, with the exception of color additives, which must be shown to be safe, the burden of proof is on the FDA to demonstrate violations of this provision.

The FDA does not review the safety of cosmetic products or cosmetic ingredients before they are marketed. It cannot require manufacturers to do safety testing of products before they are marketed and has no reporting requirements. The FDA maintains a voluntary data collection program. Cosmetic companies that wish to participate forward data to the agency. If the FDA wishes to remove a cosmetic product from the market, it must first prove that the product may be injurious to users, improperly labeled, or otherwise violates the law.

In addition to the FDCA, the Fair Packaging and Labeling Act requires labeling of ingredients on cosmetic products offered for sale, but not those used in professional salons or given away. Unfortunately, fragrances that are claimed to be protected by trade secret provisions in the law do not have to identify ingredients on the label.

In 1976, the FDCA was amended to allow the agency to regulate the testing, marketing, and use of medical devices. New medical products proposed for the market must undergo pre-market testing, but the use of medical devices already on the market in 1976 and considered safe at that time was allowed to continue. New devices made of substantially the same formulations were also readily allowed entry to the market. As a consequence, phthalate-containing medical products have been on the market for over 30 years, and manufacturers claim a record of safety. What they fail to acknowledge, however, is that no one has ever studied the impacts of phthalate exposure from their products on the reproductive development of young boys. Reports of clotting disorders and cholestasis that may be attributable to DEHP exposure from medical devices are infrequently publicized or addressed. Indeed, if a medical practitioner wished to identify products containing phthalates, in most cases it would be impossible since the FDA does not require identifying labeling and manufacturers are often reluctant to disclose product formulations.

Sometimes, phthalate-containing PVC products are regulated according to the age of potential consumers. Recently, the EU banned the use of certain phthalates in PVC toys designed for the mouths of children under three. This approach is unlikely to protect children since children of all ages routinely handle products designated for older children or adults.

Despite the reality of aggregate exposures, phthalates have been regulated individually. What may appear to be a "tolerable" level of exposure to a single compound can actually contribute to an unsafe aggregate exposure. In addition, the tolerable daily intake levels are ordinarily determined by assessing the toxicity of a single compound. Presumed "safe" levels virtually never take into account other similar compounds that have additive toxic effects and to which people are regularly exposed.

## European regulatory action

Phthalates have been identified as a priority for action in Europe. In 1998, the Oslo and Paris Commission (OSPAR) listed DBP and DEHP among substances for priority action. The 13 countries named as Contracting Parties agreed to make "…every endeavor to move towards the target of cessation of discharges, emissions and losses of hazardous substances by the year 2020. We emphasize the importance of the precautionary principle in this work."[101 143] That same year, Sweden passed an Environmental Bill that states "all uses of phthalates and other plasticizers with harmful or potentially harmful effects should be phased out on a voluntary basis."[142] The phase-out of DEHP is prioritized and further measures including prohibition are to be introduced if the voluntary phase-out fails. In 1999, a PVC Strategy in Denmark included an Action Plan for reducing and phasing out phthalates in soft plastics.[102] The Plan prioritizes large uses and emissions of phthalates and includes bans, taxes, levies, subsidies, public-sector green purchasing, and eco-labeling. In 2001, the Swedish National Chemicals Inspectorate (KEMI) recommended to the Swedish Government that, "The Swedish PVC industry should continue its work to phase out DEHP and should broaden that work so as also to include DBP and BBP, insofar as these phthalates are used."[85] KEMI also recommended the "rapid phase-out of DEHP and other fertility-impairing phthalates in feed tubes for premature babies."[85]

# Alternatives to Phthalates

The reality of aggregate phthalate exposures calls for fundamental changes in chemical manufacture, use, and regulatory policies. These high production volume chemicals permeate the market in large numbers of products and contaminate people, wildlife, and ecosystems throughout the world. Speaking of DEHP-containing PVC medical devices, the Health Canada Expert Advisory Panel concluded that "The level of concern, even though the concerns are based entirely on data derived from animal research, is nevertheless too high to recognize status quo as an option."[69]

## Material substitution

Since PVC accounts for 90% of global phthalate use, converting to PVC-free materials would substantially reduce global contamination with phthalates. Alternative, inherently pliable plastics can substitute for nearly every flexible PVC product on the market today.[160] However, even if all phthalate use in PVC were eliminated, the residual use of non-PVC phthalate-containing products with which people come into contact would likely contribute to continued human exposure. For these end uses, including cosmetics, inks, adhesives, paints, and food packaging, phthalate-free alternatives can also readily be substituted.

Plastics that compete with PVC include polyolefins (polyethylene and polypropylene), ethylene vinyl acetate (EVA), polyurethane, and silicone. These plastics compete with PVC "on the cost/performance requirements" of particular applications.[81] A subclass of polyolefins, called metallocene polyolefins, is especially competitive with PVC. Metallocene polyolefins are inherently flexible and can be tailored to specific applications. They compete with PVC in flexible medical products, packaging film, wire and cable insulation, transportation, flooring, and geomembranes."[81]

## Implementing alternatives

A wide variety of companies and institutions have initiated PVC phase-out policies for all or part of their product lines. Concerns over PVC include phthalates, metal stabilizers (lead, cadmium, organotins), toxicants used during manufacturing (vinyl chloride, ethylene dichloride), toxicants generated during manufacture and disposal (dioxins, furans), performance, and its poor recyclability (less than 1 percent annually in the US).[162] Table 10 shows numerous examples from the auto industry, building and construction uses, cabling, packaging, toys, and medical products. Industry giants moving away from PVC include prominent global corporations based in Japan, the EU, and the US.

## Identifying alternatives

Alternatives to PVC products in health care and construction can be found in four online databases:

**Database on Non-PVC Products for Health Care Institutions**
*Aarhus County, Denmark*
**http://cold.aaa.dk/pvc/english/index.htm**
The database provides health care professionals with a comprehensive, easily searched, and readily available tool for identifying PVC-free products. Released online in January 2002 in English, the database includes hundreds of PVC-free products in seven categories: cleaning articles, empty packaging, hospital supplies, hospital supplies packaging, kitchen articles, kitchen articles packaging, and office supplies.

## Table 10. Examples of companies and institutions with PVC phase-out policies

| Type | Companies |
|---|---|
| Auto | Nissan (Japan), General Motors (USA), Mercedes Benz (Germany), Toyota (Japan), Opel (Germany), Honda (Japan), Ford (UK), Daimler Benz (Germany) |
| Building / Construction | Construction Res. Centre (UK), Reserve Centre (UK), Tate Gallery (UK), Krohnengen School (Norway), Society of Danish Engineers (Denmark), Nike (Netherlands), JM (Sweden), Svenska (Sweden), Anglian Water Services (UK), Eco AB (Sweden), Borastapeter (Sweden) |
| Cabling | Matsushita Electric (Japan), North German Television (Germany), Bilbao Metro System (Spain), US Navy (USA), P&O Cruises (UK), Deutsche Bahn (Germany), London Underground (UK), Eurotunnel (UK), Sumitomo (Japan), German Telekom (Germany), Nippon Telegraph (Japan), Ricoh (Japan) |
| Home / Consumer | Sony (Japan), Kinnarps (Sweden), Toppan Printing Co. (Japan), AEG Electronics (Germany), Vorwerk (Germany), Electrolux (Sweden), OBI (Germany), Ikea (Sweden), Bene (Austria), EWE Kuechen (Austria), Hennes & Mauritz (Denmark), Nike (USA) |
| Medical | Braun-Melsungen (Germany), Fresenius (Germany), Terumo (Japan), Kaiser Permanente (USA), Baxter Healthcare (USA), Catholic Healthcare West (USA), SMZ Ost Hospital (Austria), Universal Health Services (USA), Tenet Healthcare Corp (USA) |
| Packaging | The Body Shop (UK), Migros (Switzerland), Tengelmann (Germany), Nestle (Spain, France), Evian (France), Sony (EU), Wella (Germany), Neals Yard (UK), SPAR (Austria), BILLA (Austria), ADEG (Austria), LoeWA (Austria), MEINL (Austria), Matas (Denmark), Ica (Sweden), Konsum (Sweden), Waitrose (UK), Perrier (Spain), Fonvella (Spain), Bayer (Germany), Helene Curtis (USA), Den-Mat (USA), Evian (EU), Spa (Belgium), Greenseal (USA), Carlsberg Italia (Italy), VegiWash (USA), Federated Group (USA), Eagle Family Foods (USA), Proctor & Gamble (Japan), Victoria's Secret (USA), Shiseido (Japan), Henry Thayer (USA), Ito-Yokado (Japan), Simple Green (USA), Educa Sallent (Spain), IRMA (Denmark), am/pm (Japan), Lawson (Japan), Seven-Eleven (Japan), Mycal (Japan), Seiyu (Japan), Jusco (Japan), Consumers Co-operative (Japan), Daiei (Japan), Kao (Japan), Lion (Japan), Dean Foods (USA), Cargill (Brazil) |
| Toys | APRICA Kassai (Japan), McDonalds (EU, Australia), Young Epoch (Japan), Pilot Ink (Japan), Tomy (Japan), First Years (USA), Early Start (USA), LEGO (Denmark), Playmobil (Germany), Chicco (Italy), Ravensburger (Netherlands), BRIO (Sweden), Bandai (Japan), Ambitoys (Netherlands), Artbaby (Argentina), Babelito (Argentia), Grazioli (Italy), Kiko International (Spain), Little Tikes (USA), Novatex (Germany), Continua (Germany), Fashy (Germany), Mapa (Germany), Sassy Products (USA), Mattel (USA), A-One (Japan), Ampa Hispania (Spain), Tiny Love (USA), People Co. (Japan), Juguetes y Herrajes Joal (Spain), Toho (Japan), Tolico (Denmark), Giochi Preziosi (Italy), Lamaze (USA), Play by Play (Spain) |

**Sources:** [66] [70]

**Sustainable Hospitals Project, Lowell Center for Sustainable Production**
*Massachusetts, USA*
**www.sustainablehospitals.org**
The website includes lists of alternative products for: bedding covers, catheters, enteral feeding products, gloves, intravenous (IV) solutions, office products, and other products.

**Greenpeace PVC Alternatives Database: Building the Future**
**http://www.greenpeaceusa.org/toxics/vinylhouse.htm**
or
**http://www.greenpeace.org/%7Etoxics/pvcdatabase/**
The database includes alternatives to PVC in construction, for both flexible and rigid PVC applications. Flexible products covered include flooring, wall coverings, and electrical equipment.

**Healthy Building Network**
**http://www.healthybuilding.net**
See PVC section on webpage

# Conclusions

## Phthalate use:

Phthalates are produced in the millions of tons annually worldwide and used in a wide variety of consumer and industrial products. These chemicals readily escape into the environment and contaminate the world's ecosystems. Environmental contamination and direct contact with phthalate-containing products results in virtually ubiquitous human exposures.

## Phthalate toxicity:

Health effects that may result from exposure to the phthalates differ among the various individual compounds and depend on the timing and the size of the dose. Young, developing organisms are inherently more vulnerable to exposure to some phthalates. In particular, the developing male reproductive tract appears to be the most sensitive endpoint, although effects on the liver, kidneys, lungs, and blood clotting are also of concern. In animal tests considered relevant to humans, several of the phthalates, including DEHP, DBP, BBP, and perhaps DINP, interfere with male reproductive tract development and are toxic to cells in the testes responsible for assuring normal sperm and hormone production. DEP appears to have little impact on reproductive tract development but in test tube experiments alters the microscopic appearance of cells responsible for testosterone production.

## Human exposure:

Human exposure to DEHP from PVC medical devices used in patient care has been known for some time. Expert panels of the US National Toxicology Program and Health Canada, as well as the Food and Drug Administration, have recently reviewed the toxicity of DEHP and considered exposures to patients that may result from the use of DEHP-containing equipment. Each review has independently concluded that some patients are likely to be exposed to potentially unsafe amounts of DEHP while receiving medical care.

The CDC has discovered that phthalate exposures are virtually ubiquitous in the general population and that women of reproductive age experience some of the highest exposure levels to phthalates that interfere with normal male reproductive tract development.

## Public health implications:

In this report, we have attempted to summarize what is known about human exposures to phthalates and to consider the potential health impacts of exposure to real-world mixtures of these chemicals. Using a relative potency approach, based on what is known about mechanisms of action and available experimental data, it becomes clear that a large number of women of reproductive age are sufficiently contaminated with phthalates to the point of significantly increasing the risk of abnormal development in male fetuses and baby boys. Women of reproductive age who require medical care may be exposed to additional phthalates, largely DEHP, in the medical setting, that will add significantly to their existing exposure acquired from the non-medical world in which we all live. Using CDC sample data, an estimated 5% of women of reproductive age from the general population are contaminated with 75% or more of the amount of just DBP that may begin to impair normal reproductive tract development. Many of these women will also be regularly exposed to significant amounts of BBP and DEHP, so that their aggregate exposures will pose even greater risks. When any of these women requires medical care that exposes them to additional DEHP from PVC medical devices, even more is added.

Where are these phthalates coming from in the general population? No one knows for certain, but perhaps the high exposures to DBP in women of reproductive age provide a clue, at least for that

phthalate. DBP is used in a variety of cosmetic and personal care products. Recent testing identifies DBP in some hair spray, perfume, and deodorants.[159] Many nail polishes also have large quantities of DBP. Unfortunately, labeling requirements are sufficiently lax that cosmetic ingredients considered part of the fragrance need not be identified on the label. For many consumer products, however, virtually no labeling requirements exist. Moreover, a large number of synonyms used for various phthalates complicate a label search. As a result, it is extraordinarily difficult to identify phthalate-containing products and to begin to narrow down the sources of widespread general population exposures.

## "Balkanization" of chemical policy:

Chemical policy in the US is severely "Balkanized"[161] and requires major revisions. For example, the Food and Drug Administration is responsible for food contaminants (including phthalates), drug ingredients (including phthalates), medical devices (including phthalate-containing PVC products), and cosmetics (including phthalates). Unfortunately, each of these activities is a responsibility of a different division within FDA, each of which carries out its work in isolation from the others. Moreover, the enabling legislation that authorizes the Agency to monitor these various products differs considerably among food, drugs, medical devices, and cosmetics. As a consequence, when the medical device division considers the safety of exposure to DEHP, they consider only medical devices and not the real world of population-wide exposures to multiple phthalates from multiple sources. And, when the cosmetics division considers phthalates in personal care products, not only do they limit their concerns to products in their domain, but they must prove the likelihood of harm with no requirement that manufacturers will supply safety data.

When the Consumer Products Safety Commission considers the safety of phthalates in, for example, children's toys, they consider only the phthalate that may leach out of the toy when a child chews on it, and not the other phthalates that that same child may be exposed to from contaminated food, contaminated air, or medical care.

And when the Environmental Protection Agency considers whether or not to allow phthalates in a pesticide formulation, they examine those proposals one at a time, failing to consider aggregate exposures to multiple phthalates from multiple sources.

As a result, phthalates permeate the environment and contaminate large populations of people throughout the world. Phthalates are in the blood of pregnant women at levels of concern, particularly when the contaminants are considered in the aggregate. Phthalates cross the placenta and contaminate breast milk. Relevant animal tests show that phthalates interfere with normal fetal development. The length of the period of susceptibility to relatively low levels of phthalate exposure in humans is not known. But, animal tests suggest that, with respect to male reproductive tract development, boys may remain vulnerable to phthalate exposure beyond fetal life until early puberty, since testes undergo rapid change at several stages, including later childhood.[69]

## What is needed:

Manufacturers of phthalates continue to produce large amounts and sell them to product manufacturers who use them in thousands of products. Manufacturers have consistently argued that there is no evidence that anyone has been harmed by phthalates. However, as we have noted, and as confirmed by the NTP Expert Panel and FDA, no study has ever examined the impacts of phthalate exposure on the developing male reproductive tract in people. Not one.

But lack of evidence can hardly be used as evidence of safety when no one has ever looked. The increasing incidence of hypospadias, undescended testes, and testicular cancer, and declining sperm counts in the US and many other parts of the world suggests that a closer look at many reproductive tract toxicants and endocrine disruptors is urgently needed in people.[16] With respect to phthalates, however, evidence from relevant animal studies and from limited studies of non-reproductive tract impacts in hospitalized patients is sufficient to require phasing out the use of many of the phthalates. As the Health Canada panel concluded, "the status quo is not an acceptable option."

Regulatory agencies charged with protecting medical patients, public health, and the environment must substantially revise procedures and protocols to consider the potential impacts of phthalate exposures cumulatively, rather than as single chemical exposures.

Finally, phthalates serve as a case study that demonstrates the failure of current chemical policy in the US. Regulatory authority is spread among agencies that compete with one another rather than cooperate. Lines of communication are limited and infrequently used. No one agency is authorized to look at the "big picture", which can have tragic consequences. In Europe, vigorous debate is underway regarding the phase-out of the general use of many phthalates in consumer products. Public health and the environment can only be truly protected when safer materials are substituted far upstream in the manufacturing process. Humans have demonstrated the capacity to contaminate every nook and cranny of every ecosystem and every developing fetus with synthetic chemicals that can impair normal development. Now we need to demonstrate that we can change.

First, we need to recognize that a major overhaul of current regulatory policy is long overdue. Under the current framework, government approval simply does not provide adequate real-world protection from chemical exposures. The FDA, the EPA, the CPSC, and other government agencies, with necessary authorization, must begin to transform their make-believe regulatory framework into a new, science-based system that properly considers the reality of aggregate exposures to toxic chemicals and that requires meaningful pre-market testing of commercial chemicals. Second, consumers must insist on the right to know about what chemicals are in commercial products and must have unhindered access to toxicity and exposure data. Third, manufacturers can and must shift to cleaner production practices that produce cleaner, sustainable products more suited to the contemporary world and the one that we will leave to future generations.

# Appendix I. MEHP Exposures through Medical Procedures

In its safety assessment of DEHP, the FDA noted that patients are also exposed to MEHP, the highly toxic monoester metabolite of DEHP. MEHP is formed in medical products as DEHP degrades over time resulting in patient exposure to both phthalates. MEHP is formed by the action of lipases in stored blood and plasma and by hydrolysis in IV fluids. The FDA cited studies that measured MEHP in hospital patients undergoing coronary bypass, hemodialysis, and peritoneal dialysis. In addition, the Agency acknowledged that nursing infants could receive significant doses of MEHP in breast milk from mothers undergoing hemodialysis. To estimate the amount of MEHP exposure, the FDA needed to calculate the relative potency of MEHP so that its level could be expressed in terms of DEHP concentration.

## Relative potency of MEHP

The FDA used testicular toxicity to develop a relative potency calculation for DEHP and MEHP exposures from medical products.[153] First, the Agency examined the relative potency of MEHP and DEHP to cause testicular toxicity. Second, the FDA compared the abilities of the two compounds to cause maternal toxicity as a comparison. Finally, a relative potency factor of 10 was assigned to MEHP after considering the differences in experimental results. This means that the FDA considers MEHP to be 10-fold more effective in causing testicular toxicity than DEHP.

## FDA conclusions

The FDA calculated the equivalent dose of DEHP for MEHP exposure from a variety of medical procedures and then added it to the DEHP dose to yield an aggregate dose of DEHP and MEHP. The Agency found that procedures that did not exceed the tolerable intake when considering only DEHP still did not exceed it when considering both DEHP and MEHP. However, the data shows that considering MEHP had a large impact on the dose.

Table 11 shows that infusion of crystalloid solutions is far below the tolerable intake when only DEHP is considered. However, when both DEHP and MEHP are considered, the biologically relevant dose increases by 30-fold and draws much closer to the tolerable intake. In addition, several procedures that were less than the tolerable intake when only considering DEHP exposure, became close to the limit when MEHP was considered. These procedures include replacement transfusions in neonates and orthotopic heart transplants.

The FDA decided not to account for aggregate exposures to DEHP and MEHP using the relative potency method. The Agency stated that "because of uncertainties associated with the relative potency of DEHP:MEHP and resulting estimates of DEHP equivalent dose, the TI/Dose ratios based on the dose of DEHP-equivalents received by patients will not be used to support regulatory decision making."[153]

## Limitations of the FDA approach

In determining the relative potency of MEHP, the FDA made certain value judgments. The variation seen in potencies derived from studies with a testicular endpoint ranged from 2 to more than 1,000. Potencies derived using maternal effects in mice varied from 2 to 80.[153] The Agency chose a value of 10 using the testicular endpoint. The authors of this report illustrate the quantitative consequence of this decision in Table 12.

Table 12 shows that choosing a mid-range relative potency for MEHP of 80 instead of 10 significantly increases the DEHP-equivalent dose calculated for various medical procedures. In fact, using the higher relative potency number increases the DEHP-equivalent dose of DEHP + MEHP by 2 – 8 fold. The result influences judgments about the safety of various procedures as shown below.

## Table 11. Tolerable intake compared to DEHP and DEHP+MEHP

| Procedure | TI/DEHP | TI/DEHP+MEHP |
|---|---|---|
| Infusion of IV crystalloid solutions | 120 | 4.44 |
| Adult transfusion /ECMO | 0.2 | 0.03 |
| Neonate exchange transfusion | 0.03 | 0.02 |
| Neonate replacement transfusion | 2.0 | 1.75 |
| CABG cardiopulmonary bypass | 0.6 | 0.30 |
| Orthotopic heart transplant | 2.0 | 1.00 |
| Artificial heart transplant | 0.25 | 0.12 |

**Data source:** [153] **Abbreviations:** TI: tolerable intake.
See the Health Care Without Harm website for updates to this table: **http://www.noharm.org**

## Table 12. DEHP equivalent doses for various medical procedures depending on MEHP relative potency value. Doses in mg/kg/day.

| Procedure | DEHP | MEHP | RPF = 10 DEHP equivalent | RPF = 80 DEHP equivalent |
|---|---|---|---|---|
| Infusion of IV crystalloid solutions | 0.005 | 0.013 | 0.14 | 1.0 |
| Adult transfusion /ECMO | 3.0 | 2.0 | 23 | 163 |
| Neonate exchange transfusion | 22.6 | 0.68 | 29 | 77 |
| Neonate replacement transfusion | 0.3 | 0.0043 | 0.34 | 0.64 |
| CABG cardiopulmonary bypass | 1.0 | 0.1 | 2.0 | 9.0 |
| Orthotopic heartTransplant | 0.3 | 0.03 | 0.6 | 2.7 |
| Artificial heart transplant | 2.4 | 0.26 | 5.0 | 23 |

**Data source:** [153] **Abbreviations:** RPF: relative potency factor.
See the Health Care Without Harm website for updates to this table: **http://www.noharm.org**

The consequence of choosing a different relative potency for MEHP can be seen by comparing the aggregate dose of DEHP and MEHP released to patients during various medical procedures. Table 12 shows that a relative potency of 80 significantly changes the total exposure to patients.

When considering only DEHP exposure, infusion of IV crystalloid solutions has TI/DEHP ratio of 120 indicating that the DEHP dose is far below the TI. If MEHP is added to the dose consideration by using relative potency of 10, the ratio becomes 4.44. In contrast, when a relative potency of 80 is used, the ratio becomes 0.57. Under these conditions, infusion of crystalloid IV solutions would exceed the tolerable intake. In fact, all the procedures in Table 13 show a DEHP-equivalent dose that exceeds the tolerable intake if a relative potency of 80 is used instead of 10 to calculate the added impact of MEHP.

**Table 13. Tolerable intake compared to DEHP and DEHP+MEHP doses using different relative potency factors.**

| Procedure | TI/DEHP | RPF = 10 TI/DEHP+MEHP | RPF = 80 TI/DEHP+MEHP |
|---|---|---|---|
| Infusion of IV crystalloid solutions | 120 | 4.44 | 0.57 |
| Adult transfusion /ECMO | 0.2 | 0.03 | 0.00 |
| Neonate exchange transfusion | 0.03 | 0.02 | 0.01 |
| Neonate replacement transfusion | 2.0 | 1.75 | 0.93 |
| CABG cardiopulmonary bypass | 0.6 | 0.30 | 0.07 |
| Orthotopic heart transplant | 2.0 | 1.00 | 0.22 |
| Artificial heart transplant | 0.25 | 0.12 | 0.03 |

**Data source:** [153] **Abbreviations:** RPF: relative potency factor; TI: tolerable intake.
See the Health Care Without Harm website for updates to this table: **http://www.noharm.org**

## Exposures from medical procedures exceed tolerable intake

The FDA Safety Assessment of DEHP Released from PVC Medical Devices reveals several procedures that expose patients to levels of DEHP close to the tolerable intake. When MEHP is also considered, the exposures provided even by common medical treatments such as IV infusions can draw close to or exceed the tolerable intake depending on the relative potency of MEHP used to calculate the aggregate exposure. This is in addition to the aggregate exposures to other phthalates calculated above.

# Appendix II. Phthalate Toxicity

The toxicity of phthalates to mammals is shown in Table 14. Note that these effects are dose-dependent and that humans are not necessarily exposed to the levels that elicit these effects in animal studies. Impacts also depend on the route of exposure, species differences in metabolism, distribution, excretion, and tissue sensitivity. Critical windows of vulnerability during development significantly influence both the dose required to elicit an impact and the nature of the impact.

**Table 14. Toxicity of phthalates to various mammalian organ systems Part 1 of 4**

| Organ | Phthalate | Species | Effect | Study |
|---|---|---|---|---|
| **Adrenal gland** | DEP | Rat | Elevated organ weight | 19 |
| | DHP | Mouse | Decreased organ weight | 92 |
| **Bone** | BBP | Rat | Reduced bone marrow cellularity | 2 |
| **Brain** | BBP | Cerebellar explants newborn rat | Inhibit outgrowth of nerve fibers and glial cells in vitro | 84 |
| | DEP | Rat | Increased weight | 19 |
| **Blood** | BBP | Rat | Myelomonocytic leukemia | 89 |
| | DBP | Human lymphocytes in vitro | DNA damage to lymphocytes | 88 |
| | | Mouse | Anemia | 112 |
| | DIBP | Human lymphocytes in vitro | DNA damage to lymphocytes | 88 |
| | DINP | Rat | Mononuclear cell leukemia, reduced white blood cell counts | 20 |
| | | Rat | Decreased hemoglobin, decreased number of red blood cells | 150 |
| **Fetus/Embryo** | BBP | Rat | Increased post-implantation loss; deformed vertebral column and ribs, cleft palate, fused sternebrae | 40 |
| | | Rat | Reduced pup weight at birth | 64 |
| | DBP | Rat | Reduced fetal weight, increased resorptions, increased skeletal defects | 121 |
| | | Rat | Embryo-fetal death, decreased fetal weight | 39 |
| | | Rat | Birth defects in the prosencephalon, the optic system, and the mandibular and maxillary processes | 130 |
| | | Rat | Transferred to placenta and embryo | 130 |
| | | Rat | Increased post-implantation loss; deformed vertebral column and ribs, cleft palate, fused sternebrae | 40 |
| | | Mouse | Decreased fertility, fewer litters per pair, fewer pups per litter, fewer pups born alive | 92 |

## Table 14. Toxicity of phthalates to various mammalian organ systems
## Part 2 of 4

| Organ | Phthalate | Species | Effect | Study |
|---|---|---|---|---|
| **Fetus/Embryo** | DEP | Mouse | Reduced pup size in offspring | 92 |
| | | Rat | Increased incidence of supernumerary ribs | 52 |
| | DHP | Mouse | Decreased fertility, decreased number of litters per pair, decreased number of live pups per litter, decreased number of pups born alive | 92 |
| | DIDP | Rat | Skeletal defects in the fetus | 155 |
| | | Rat | Reduced offspring survival in both generations | 75 |
| | DINP | Rat | Reduced pregnancy weight gain | 64 |
| | | Rat | Skeletal and visceral birth defects, reduced offspring viability and weight gain | 114 |
| | MBP | Rat | Birth defects in the prosencephalon, the optic system, and the mandibular and maxillary processes in vivo; growth retardation, dysmorphogenesis in vitro | 130 |
| | | Rat | Deformed vertebral column, deformed ribs, dilation of renal pelvis, cleft palate, fused sternebrae | 38 |
| | | Rat | Increased pre- and post-implantation loss, impaired uterine function | 43 |
| | MEHP | Rat | Maternal lethality, litter resorption, reduced fetal weight | 129 |
| | | Rat granulosa cells | Inhibition of estradiol production | 34 |
| **Heart** | DEHP | Isolated rat heart | Decrease in heart rate | 119 |
| | DEP | Rat | Increase in heart weight | 19 |
| | MEHP | Rat | Decrease in heart rate and blood pressure | 126 |
| **Kidneys** | DBP | Rat | Causes renal cysts | 158 |
| | DEHP | Rat | Reduction in creatinine clearance; cystic changes | 27 |
| | DHP | Mouse | Decreased organ weight | 92 |
| | DINP | Rat | Transitional cell carcinoma | 20 |
| **Liver** | DBP | Rat | Decreased transferrin levels, increased haemosiderin levels | 58 |
| | | Rat | Activate laurate hydroxylation in vitro | 118 |
| | | Rat | Inhibit mitochondrial respiration; peroxisome proliferation | 4 |
| | DEHP | Rhesus monkey | Abnormalities in histology, reduction in liver function | 87 |
| | | Rat, Mouse | Hepatocellular carcinoma | 89 |
| | | Rat | Hepatocellular adenoma | 105 |
| | DEHP | Rat liver microsomes | Activate laurate hydroxylation in vitro | 118 |
| | DEP | Rat | Abnormal enzyme levels, elevated cholesterol and triglyceride levels. | 139 |
| | DIDP | Rat | Abnormal enzyme levels, reduced cytoplasmic basophilia, increased eosinophilia | 17 |
| | | Rat | Altered pathology, peroxisome proliferation | 95 |

## Table 14. Toxicity of phthalates to various mammalian organ systems Part 3 of 4

| Organ | Phthalate | Species | Effect | Study |
|---|---|---|---|---|
| **Liver** | DINP | Rat | Carcinoma and adenoma | 20 |
| | | Rat | Spongiosis hepatitis | 150 |
| | DMP | Rat | Increased organ weight in females | 52 |
| **Lungs** | DEHP | Human pre-term infants | Respiratory distress, pathological changes similar to hyaline membrane disease | 128 |
| | DIDP | Rat | Increased width alveolar septa, inflammatory reactions, increased numbers macrophages and pneumocytes | 60 |
| **Mucosa** | DBP | Human lymphocytes | DNA damage | 88 |
| | DIBP | Human lymphocytes | DNA damage | 88 |
| **Ovaries** | DINP | Rat | Reduced organ weight | 114 |
| | BBP | Rat | Reduced organ weight | 109 |
| | MEHP | Rat granulosa cells | Reduced estradiol production in vitro | 97 |
| **Pituitary** | DEP | Rat | Elevated organ weight | 19 |
| **Prostate** | BBP | Rat | Atrophy of the prostate | 2 |
| | DEP | Mouse | Increased weight | 92 |
| | DBP | Rat | Absent or partially developed ventral prostate | 108 |
| | DEHP | Rat | Anterior prostate agenesis | 104 |
| **Spleen** | DBP | Rat | Increased hemoglobin, ferritin, and haemosiderin levels | 58 |
| **Developmental/ reproductive effects** | BBP | Rat | Male infants with female-like areolas/nipples; shortened anogenital distance; reduced testis weights, reproductive malformations in males | 64 |
| | | Rat | Decreased testosterone, increased FSH | 109 |
| | BBP | Rat | Reduced fetal testis weights, increased retarded testicular descent | 121 |
| | | Rat | Reduced sperm production, reduced testis weight | 134 |
| | | Rat | Atrophy of the testis, seminal vesicles; decreased testosterone, increased FSH and LH; immature sperm cells | 2 |
| | DBP | Rat | Fetuses with undescended testes; decreased anogenital distance in male infants | 42 |
| | | Rat | Hypospadias; absent or partially developed epididymis, seminal vesicles, reduced weights of testis components; seminiferous tubule degeneration, interstitial cell hyperplasia and cell adenoma | 108 |
| | | Rat | Decreased mating, fertility, pregnancy | 157 |
| | | Human sperm | Decreased sperm mobility in vitro | 56 |
| | | Rat | Leydig cell adenomas in male offspring; fetal rats with decreased testosterone levels and increased Leydig cell numbers | 54 |

## Table 14. Toxicity of phthalates to various mammalian organ systems Part 4 of 4

| Organ | Phthalate | Species | Effect | Study |
|---|---|---|---|---|
| **Developmental/ reproductive effects** | DBP | Human sperm | Decreased sperm density in university students with DBP in semen | 106 |
| | DEHP | Rat | Disorganization of seminiferous tubule structure in male offspring | 8 |
| | | Rat | Sertoli cell vacuolation; atrophy of seminiferous tubules; loss of spermatogenesis | 124 |
| | | Rat | Testicular, epididymal atrophy, and testicular agenesis; hemorrhagic testes; hypospadias in male offspring | 65 |
| | | Rat | Male infants with female-like areolas/nipples, shortened anogenital distance, reduced testis weights, reproductive malformations in males | 64 |
| | | Rat | Induction of Leydig cell tumors | 12 |
| | | Human sperm | Decreased sperm mobility in vitro | 56 |
| | DEP | Rat | Sertoli cell/gonocyte detachment in vitro | 94 |
| | | Mouse | Decreased sperm concentration | 92 |
| | | Rat | Increased testes weights | 19 |
| | | Rat, Leydig cell culture | Alteration in Leydig cell structure | 82 |
| **Testes** | DHP | Mouse | Decreased fertility, decreased percentage of mobile sperm, decreased sperm concentration; decreased weights of testis, epididymis, and seminal vesicles; atrophy of seminiferous tubules | 92 |
| | DINP | Rat | Male infants with female-like areolas/nipples; reproductive malformations in male infants | 64 |
| | | Rat | Increased testes weights | 114 |
| | | Rat | Testicular hyperplasia, testicular tumors | 150 |
| | DPP | Rat | Altered testicular enzymes, decreased progesterone binding | 55 |
| | MEHP | Rat Sertoli cells | Inhibits FSH-stimulated cAMP accumulation in Sertoli cells in vitro; increases lactate secretion; decreases ATP levels in vitro | 7 |
| | MBP | Rat Sertoli cells | Inhibits FSH-stimulated cAMP accumulation in Sertoli cells in vitro; | 71 |
| | MPP | Rat Sertoli cells | Inhibits FSH-stimulated cAMP accumulation in Sertoli cells in vitro; increases lactate secretion | 71 |
| **Thymus** | BBP | Rat | Thymus atrophy | 2 |
| **Thyroid** | DEP | Rat | Elevated organ weight | 19 |
| **Uterus** | BBP | Rat | Decreased uterine decidual growth | 44 |
| | | Rat | Decreased uterine weight, decreased progesterone levels | 41 |
| | DBP | Mouse | Decreased weight | 92 |
| | DINP | Rat | Endometrial hyperplasia and fibrous thickening; endometrial adenocarcinoma | 150 |

See the Health Care Without Harm website for updates to this table: **http://www.noharm.org**

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160. For example, substitutes are widely available for most PVC products used in health care. A notable exception is for packaging red blood cells. Here, PVC offers a unique advantage: DEHP acts as an unregulated preservative of red blood cells.The US Food and Drug Administration does not regulate DEHP as an additive. Baxter International, a leading producer of DEHP-softened PVC red blood cell bags, also markets a non-DEHP-softened red blood cell bag, which uses butyryl-trihexyl citrate as a plasticizer. Both bags preserve red blood cells for the same length of time. *Plastics Week*, "Citrus-Based Plasticizer to Replace DEHP in Big Medical Applications", 2/10/92.

161. If globalization is the increasing interconnectedness of peoples and places through converging processes of economic, political, and cultural change, then balkanization is a counteraction to the integrating and homogenizing effects of globalization. Whereas globalization acts as connective mechanism… balkanism refers to fragmentation and separation. Taking its name from the divisive and conflict-ridden Balkan region of Europe, balkanization has come to refer to any region in the world faced with internal turmoil and schisms, in this case, the regulatory structure and safety net for phthalate exposure. See http://www.countrywatch.com/@school/balkanization.htm for more information on 'balkanization'.

162. The recycling rate was determined based on the vinyl industry's estimate of 18 million pounds of PVC recycled per year. Jebens (1997), estimated PVC consumption at 18 billion pounds per year, bringing us to am estimate of less than 1%.

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