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Phthalates and Human Health:
Demystifying the Risks of Plastic-softening Chemicals

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Executive Summary

People are increasingly concerned about the safety of their food, water, consumer, and medical products. Groups such as Greenpeace and Health Care Without Harm have suggested that chemicals used to soften normally-rigid PVC, or polyvinyl chloride plastics, pose a threat to human health, and should be banned. Other groups, such as a task force headed by former U.S. Surgeon General C. Everett Koop, argue that the risk posed by these chemicals is minimal, since dosage levels are low, and claim significant health benefits directly related to their use.

Greenpeace, for example, suggests that two such chemicals, called phthalates (pronounced thall-eights), are suspect as human cancer-causing agents, could damage the liver and kidneys, might damage the development of reproductive organs, and might interfere with development by acting as a mimic of the sex hormone estrogen.

Some regulatory groups, such as the U.S. Consumer Product Safety Commission and the National Institute of Health's Center for the Evaluation of Risks to Human Reproduction are also concerned about one phthalate, with a chemical abbreviation of DEHP. Their concern stems from the fact that maximally exposed humans can receive (for a short term) a dose close to that seen to cause adverse effects in animals (when administered over a lifetime). Specifically, infants undergoing certain types of medical treatment receive doses that exceed the common regulatory threshold, designed to insure that human exposures never exceed one-hundredth of the dose of a chemical shown capable of causing any harm to any animal.

DEHP, DINP (a second type of phthalate), and other phthalates have indeed been shown to cause various harms to experimental animals when administered at high doses. But the key determinant of human risk is the dose. In the vast majority of cases, human exposures to phthalates fall far short of the experimental doses shown to cause harm to animals, often by orders of magnitude. For DEHP, a plasticizer used in manufacturing medical devices, the difference between human doses and harmful animal doses are generally large:

- While a lifetime DEHP dose of 200 milligrams per kilogram of body weight per day can cause shortened lifespans or weight loss in rats, people at the high end of DEHP exposure (via dialysis) get a short term dose that is 28 times less.

- While a lifetime DEHP dose of 50 milligrams per kilogram of body weight per day can cause low level cancerous changes and liver enlargement in rats, people at the high end of DEHP exposure (via dialysis) get a short term dose that is seven times less.
- While a lifetime DEHP dose of 400 milligrams per kilogram of body weight per day can cause liver tumors in rats, people at the high end of DEHP exposure (via dialysis) get a short term dose that is 56 times less.
- Even the maximally exposed human being, a child receiving a life-saving treatment called extracorporeal blood oxygenation, is exposed—for only a short time—to a dose that is 70 percent of the lifetime dose shown to cause a low level of observed health hazard in rats.

For DINP, a plasticizer used in manufacturing softened-vinyl toys or products for children (and once, but no longer used to manufacture pacifiers or chew-toys), the situation is similar: while animal tests suggest that high dosages, administered over long time periods can cause various types of harm to experimental animals, humans are exposed to doses that are far lower, and for far shorter periods of time.

- While a lifetime dose of 88 milligrams per kilogram of body weight per day led to only a low level of observed adverse health impacts to male rats, maximally exposed humans (children using pacifiers for two years) would be exposed to a dose which is over 6,000 times less.

Beyond the simple question of dose, other factors suggest that humans are likely to be less sensitive to phthalates than test animals are, even if exposures were at comparable levels. Human exposure pathways, metabolic processes, exposure frequency and duration are almost always different than those of experimental animals shown to suffer damage in toxicological testing.

Finally, the question of benefits is relevant in any holistic assessment of the risk-altering impacts of proposed regulations. The number of Americans currently receiving benefits from the use of phthalate softened vinyl is substantial: In 1996, 31.5 million outpatient surgeries and 40.3 million inpatient surgeries were performed. If phthalate-softened PVC products are used in only half of all surgeries (a very conservative estimate), nearly one-third of the population derives a health benefit from them in any given year.

Whole blood stored in a PVC bag remains viable for 42 days, compared to only 21 days for other containers. According to America's Blood Centers, more than 23 million blood components are made from about 14 million whole blood donations (stored in PVC bags) yearly.

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What Are Phthalates, and Why Do We Need a Plain-English Guide?

Increasingly, issues of public and environmental health involve complex scientific issues that neither the public nor policymakers have the time or energy to study in depth. Advocacy groups publish materials promoting one side of a policy issue or the other, but generally present only the scientific evidence that supports their policy proposal. Rarely do issue-advocacy groups attempt to paint a balanced picture with suitable detail to allow for meaningful policy consideration or discussion. Scientific review bodies and blue-ribbon commissions strive for more balanced portrayal of scientific evidence (and often do so very well), but they rarely translate that information into language that the interested lay reader or policymaker can understand. The growing debate over regulation of vinyl plasticizers, or phthalates (usually pronounced thall-eights) is one such issue.

Phthalates render what would otherwise be rigid plastic into flexible vinyl. Linking together individual molecules of vinyl chloride produces solid polyvinyl chloride (PVC) plastic. Without the addition of other chemicals, called plasticizers, PVC is a hard, relatively inflexible plastic. If plasticizers are added before the final product is made, a wide variety of softer plastics can be produced from the vinyl chloride stock.

The most commonly used vinyl plasticizers are diethylhexyl phthalate (DEHP) and diisononyl phthalate (DINP). DEHP is most commonly used in manufacturing vinyl medical devices, while DINP is most commonly used in manufacturing vinyl children's products, construction materials, and other consumer products.

Several advocacy groups have suggested that exposure to phthalates in consumer products and medical devices poses a health risk, particularly to children. These groups have called for their banning through regulatory action. A group called Health Care Without Harm has campaigned against phthalate use in medical devices, as has Greenpeace. Greenpeace and the National Environmental Trust have also campaigned against the use of phthalates in children's products. These groups interpret tests performed on animals as suggesting that phthalates—two phthalates in particular—pose similar hazards to humans at low dose/short-term exposure as they do to animals exposed to high-dose/long-term exposure. Greenpeace, for example, suggests that phthalates are suspected as human cancer-causing agents, could damage liver and kidneys, might damage the development of reproductive organs, and might interfere with development by acting as a mimic of the sex hormone estrogen. A study commissioned by Health Care Without Harm concluded that humans are exposed to substantial levels of DEHP through medical devices. Citing various animal studies, the authors conclude: "Inadequate evidence exists to conclude that the toxic mechanisms found in laboratory animals do not occur in humans."

Other groups have disputed some or all of these claims, including: 1) the U.S. Consumer Product Safety Commission (CPSC); 2) an expert panel chaired by former U.S. Surgeon General C. Everett Koop and convened by the American Council on Science and Health (ACSH); 3) the United Nations International Agency for Research on Cancer (IARC), and 4) the authors of a comprehensive review of phthalate toxicology published in the authoritative *Critical Reviews in Toxicology*. In the latter study, Wolfgang Huber and his associates conclude that "an actual threat to humans by DEHP seems rather unlikely." The CPSC staff found that the estimated human exposure was below the acceptable daily intake or level of concern. The CPSC concluded that "few, if any, children are at risk from liver or other organ toxicity from the release of DINP from these [teethers, rattles and toys made from PVC] products." They stopped short of giving DINP a clean bill of health, however, suggesting additional study of the cancer-causing potential of DINP.

The ACSH report by C. Everett Koop, Juberg et al., takes a broader view of the question of risk, pointing out that even if phthalates pose some risk to human health, such risks need to be assessed alongside of the health benefits that phthalates provide. Such benefits, according to the ACSH report include higher quality medical devices available to more people at less cost than alternatives, and the preservative effect that phthalates exert on the supply of blood in the United States. The ACSH report concludes that "DEHP in medical devices is not harmful to even highly exposed people. . . ," and suggests that DEHP "imparts a variety of important physical characteristics that are critical to the functioning of medical devices, and eliminating

DEHP in these products could cause harm to some individuals." On DINP, the ACSH report is somewhat more ambivalent, concluding that "much of the evidence [for DINP's harmfulness] has little relevance to humans, and that DINP in toys is not harmful for children in the normal use of these toys." The panel recommends detailed studies of DINP use in mouthing toys or substances that children might normally mouth or chew on.

Most recently, the United Nation's International Agency for Research on Cancer (IARC) downgraded the classification of DEHP from a "possible" human carcinogen to "Cannot be classified as to its carcinogenicity in humans."

As can be seen from the approach taken in expressing the risks, the groups discussed above view the question of risk in very different lights, which shapes which information they feel should be considered in determining risk. Greenpeace, Health Care Without Harm, and similar advocacy organizations invoke a regulatory approach often called the precautionary principle, which presumes that chemicals are likely to cause harm and must be proven innocent. Information suggesting a risk is considered meaningful, but exculpatory data is rarely given equal weight. One potential risk of this approach is the potential for regulatory overload, where all chemicals are to be regulated by default, and only permitted for specific uses after demonstrations of harmlessness.

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Most U.S. regulatory agencies eschew this approach, and use an approach similar to the authors of the CPSC study, employing a standard scientific risk-assessment approach (though still one focused only on risk and not on benefit). In such a framework, a chemical might warrant regulatory control if evidence supports the contention that the chemical is capable of causing harm to human beings at a relevant level of exposure. Further, most regulatory agencies (and others favoring "conservatism" in risk assessment) hold that a chemical which proves harmful in animal testing is suspected of potential human harm unless exposure levels are 100 times lower for even the most highly exposed humans. In the case of phthalates, human exposures for highly exposed individuals receiving medical treatment do not always meet this conservative test of safety.

Finally, analysts such as those authoring the ACSH report take an agency-like approach to evaluating risk, but may not hold with as high a degree of conservatism. Further, they tend to invoke a more holistic view of risk, suggesting that meaningful risk assessments must consider benefits and potential tradeoffs as well as risks.

But how is the lay public to choose between the various perspectives and policy proposals? Making sound policy judgements about issues like phthalates, climate change, pesticide exposures, the ozone hole, and so on requires more than just cursory understanding of the subject.

As the late policy analyst Aaron Wildavsky demonstrated, formulating policy without a solid understanding of both the certain and uncertain elements of a potential risk wastes resources, invites unintended consequences, and generally makes for policy that does more harm than good.

This guide is designed to help policymakers, the media, and the interested public gain a deeper understanding of the certainties and uncertainties in our scientific understanding of the risk posed by vinyl plasticizers, so that they can decide which perspective they feel is most applicable and useful in the formation of public policy.

Part 2

Where are Vinyl Plasticizers Used?

Softened vinyl products manufactured with phthalates (and used in the United States) include an array of consumer and medical products:

Consumer Products	
• Vinyl clothing	Emulsion paint
Footwear	Printing inks
Non-mouthing toys and children's products	Product packaging and food wrap
Vinyl flooring	
Medical Devices	
• Blood bags and tubing	Pressure monitoring tubing
IV containers and components	Cannulas
Surgical Gloves	Breathing tubes
General purpose labware	Inhalation masks
Inflatable splints	Bed pans, basins, and bed rails
Thermal blankets	Catheters
Thermoformed plastic trays	Device packages
Dialysis tubing	Drip chambers
Nasogastric tubing	Enema tips

Different phthalates are used to create the different products listed above. Besides DEHP and DINP, other phthalates include Butyl Benzyl Phthalate (BBP), Diisodecyl Phthalate (DIDP), di-n-octyl phthalate (DNOP), di-n-Hexyl Phthalate (DNHP), and di-n-butyl phthalate (DBP).

The final content of phthalate in the finished plastic product varies depending on the product but ranges from 10 percent to 60 percent of the product mass on a weight basis.

Part 3

How are Humans Exposed to

Vinyl Plasticizers?

Humans can be exposed to vinyl plasticizers through ingestion, inhalation, direct injection, or by skin contact. But exposure is only a small part of the story: absorption rates vary dramatically among the different exposure pathways and among different animal species as well. In addition, the ingested, inhaled, injected, or absorbed chemical can undergo different types of chemical modification along the path of entry or travel through the body, changing the potential effect it has on the various tissues and organs of the body.

Exposures to phthalates, as with most other chemicals, is expressed as a ratio of the exposure to the body weight of the exposed organism. Exposures to phthalates range from milligrams (thousandths of a gram) to micrograms (millionths of a gram). Body weights for exposed humans range from about 11 kilograms (a five-pound baby) to well over 100 kilograms (220 pounds) for an adult.

The dose is a ratio of the weight of administered substance, to the weight of the organism receiving it. Thus, if a 70 kilogram person (154 pounds) were exposed to 500 milligrams of lanolin each day, the exposure would be 500 milligrams/70 kilograms of body weight, or about 7 milligrams/kilogram of body weight per day. This would be abbreviated as 7 mg/kg-b.w./dy.

But one has to keep in mind that the exposure does not necessarily equal the dose. In most cases, one only absorbs some of whatever chemical one is exposed to, rather than all of it. So, if one were **exposed** to the same 500 milligrams of lanolin, but only absorbed 10 percent of it into the bloodstream, the actual **dose** that might reach, say, the liver, would only be 50 mg/kg-b.w./dy.

For comparison purposes, these are some typical daily dosages that a 70 kilogram human might receive:

- An 81 mg therapeutic aspirin tablet ?@ ?1 mg/kg-b.w./dy
- 500 milligrams of vitamin C ??@ ?7 mg/kg-b.w./dy
- 650 mg of aspirin (2 regular tablets) ?@ ?9 mg/kg-b.w./dy

A. Inhalation

Humans (and other animals) can absorb phthalates through the lungs. Table 1 shows the airborne exposure to DEHP that people could encounter and the actual dose they might absorb (assuming 100 percent absorption). Phthalates are not absorbed at 100 percent, via inhalation, however. Studies suggest that in rats, for example, less than 25 percent of the phthalate concentration of inhaled air is actually absorbed. Inhaled DINP exposure has rarely been measured, but exposure rates are probably comparable to DEHP.

Table 1: Airborne DEHP Concentrations

Source of Exposure	Dose in mg/kg of body weight/d
• Air (worst case)	0.100
• Air (indoor, PVC paved room)	0.014-0.086

• Air (in cars at 60° C)	.030
• Air (in cars at 25° C)	<.0001
• Air (outdoor, urban)	0.000006-0.0000225
• Air (outdoor, non-urban)	» 0

Source: Wolfgang Huber et al., "Hepatocarcinogenic Potential of Di(2-ethylhexyl)phthalate in Rodents and its Implications on Human Risk," *Critical Reviews in Toxicology*, vol. 26, issue 4 (June 1996). Conversion from micrograms/kilogram of body weight/day by author.

Humans can also be exposed to inhalable phthalates when they receive inhalation therapy, or other treatments involving inhalation of gases, such as anesthetic delivery. Information on such exposures is scarce, but one study suggested that such exposures do occur (particularly in infants on forced-air ventilation devices), and may pose a risk to the health of such patients.

B. Ingestion

Humans also ingest a small quantity of phthalates in food, water, and during certain medical treatments that place vinyl products into the mouth, esophagus, or stomach. Table 2 shows the typical ingested DEHP or DINP exposures that people might encounter and the actual dose they might absorb (assuming 100 percent absorption).

Table 2: Ingested DEHP/DINP Concentrations	
Source of Exposure	Dose in mg/kg of body weight/dy
DEHP	
• Food (hypothetical worst case)	0.485
• Food (typical situation)	0.025
• Mouthing toys	0.00024-0.00166
• Drinking water	<0.001
DINP	

• Mouthing toys (3-12 months old, worst case)	0.0943
• Mouthing toys (13-26 months old, worst case)	0.0076

Source: DEHP values from Wolfgang Huber et al., "Hepatocarcinogenic Potential of Di(2-ethylhexyl)phthalate in Rodents and its Implications on Human Risk," *Critical Reviews in Toxicology*, vol. 26, issue 4 (June 1996). DINP values from Michael A. Babich, *The Risk of Chronic Toxicity Associated with Exposure to Diisononyl Phthalate (DINP) in Children's Products* (Washington, D.C.: United States Consumer Product Safety Commission, December 1998) (http://www.cpsc.gov/ phth/dinp.html). Conversion to percent of body weight per day from micrograms/kilogram of body weight/day by author.

C. Direct Injection

Medical procedures can also expose humans to the direct introduction of phthalates into the bloodstream. Table 3 shows the typical injected or infused DEHP exposures that people could encounter and the actual dose they might absorb (assuming 100 percent absorption) in a variety of medical procedures involving direct injection of substances into the bloodstream.

Table 3: Injected / Infused DEHP Exposures and Potential Doses

Source of Exposure	Dose in mg/kg of body weight per treatment
DEHP (long term)	
• Hemodialysis, one session	0.01-7.2
• Peritoneal dialysis	0.800
• Clotting factors in hemophiliacs	0.030
DEHP (short term, < 10 days)	
• Extracorporeal oxygenation in infants	42-140
• Adult blood transfusion	0.2-8.5
• Newborn blood transfusion	0.5-4.2

• Platelet concentrates in adults	0.4-2.5
• Cardiopulmonary bypass	0.3-2.4
• Platelet concentrates in newborns	1.9

Source: Wolfgang Huber et al., "Hepatocarcinogenic Potential of Di(2-ethylhexyl)phthalate in Rodents and its Implications on Human Risk," *Critical Reviews in Toxicology*, vol. 26, issue 4 (June 1996). Conversion to milligrams/kilogram of body weight per day from micrograms/kilogram of body weight/treatment by author.

D. Skin Absorption

In a test of skin penetration, where a phthalate solution was painted onto the skin of a laboratory rat, 86 percent of the chemical stayed on the skin and was not absorbed, even after seven days. Other tests suggest that human skin is even less permeable to phthalates. Assuming a person were to wear gloves with a 30 percent PVC content for two hours per day, the worst-case exposure would be 0.027 mg/kg-b.w./dy.

Part 4

Interpreting Animal Test Results

DEHP and DINP have been tested on a variety of animals, including rats, mice, rabbits, monkeys (macaque, marmosets, and rhesus), dogs, and cats. Studies of phthalate's cancer-causing potential were first conducted in the 1950s when long-term exposure tests were conducted using rats and dogs. The animals were fed DEHP doses of up to 0.025 percent of their total body weight for several years. The study found no evidence of increased tumor growth.

The current concern that phthalates might be able to cause cancer stems, in part, from a 1982 study by the National Toxicology Program. Looking at dose rates nearly four times higher than the early studies (up to 0.09 percent of body weight), the NTP study found that some rats and mice developed liver tumors when exposed to high doses of DEHP over the majority of their normal life span. Subsequent studies have added substantially to our understanding of phthalate toxicity.

Before reviewing the findings of such studies, however, some discussion of the relevancy and applicability of animal test results to evaluating health risks to human beings is in order. Gathering animal-test data is only the beginning of a meaningful process of assessing risk—many other factors have to be considered, reflective of the many differences between human beings and other animals.

A. Exposure Pathways Often Differ

The exposure pathway is an important element in understanding the potential toxicity or cancer-causing activity of a

chemical. In animal studies, different exposure pathways can be used to illuminate different potential risks and to account for different biochemical conditions that the chemical might encounter as it passes through the body. To examine the impacts on the digestive system, for example, the chemical might be administered by passing a tube directly into the esophagus or stomach. If one is only concerned with the impacts of the chemical when directly injected into the blood stream, the test dose might be injected intravenously.

When interpreting animal test results, it is also important to consider whether humans are likely to be exposed to comparable levels of a chemical through the same pathway that was tested in the animals studied. The length of exposure also matters, since short-term impacts are not necessarily related to long-term effects, and vice verse. Finally, the age of the animal during testing matters. As Huber, et al. point out, studies of testicular toxicity in rats, for example, were carried out on immature rats, which, because they are in a rapid growth phase, are more susceptible to testicular damage than an adult rat might be. One can see why it would be problematic to assume that the risk of testicular damage in a human exposed to a single dose of DEHP as an adult is comparable to the risk faced by an immature rat exposed to chronic, high doses of DEHP during development.

B. Different Levels of Absorption

Simply assuming that an ingested dose of chemical given to a mouse or rat is equivalent to the same dose given to a human could also lead to misunderstanding risk because different animals process chemicals differently. In rats, for example, 20 percent of the DEHP put into the digestive tract was found to have passed right out, even at low doses where saturation could not be a factor. In marmoset monkeys, absorption was even lower, with barely half of the DEHP administered absorbed through the intestine. The human digestive system may absorb even less than marmosets. Though detailed studies of the excretion of DEHP in humans feces have not been done, the percentage of administered DEHP and breakdown products passed out through the kidneys accounted for only 11 and 31 percent of the original dose. This result suggests that the remainder (70 to 90 percent) was never taken into the bloodstream at all. As mentioned above, when painted on the skin of a rat, 86 percent of the chemical stayed on the skin and was not absorbed, even after seven days, and tests suggest that human skin is even less permeable.

When interpreting animal test results, it is also important to consider whether humans are likely to be exposed to comparable levels of a chemical through the same pathway that was tested in the animals studied.

C. Different Metabolic Processing

Different animals breakdown different chemicals differently. In the case of phthalates, while it is clear that the metabolic pathway in rats and mice requires more steps than in primates or humans, it is unclear exactly how that alters the exposure of possibly sensitive tissues to DEHP, or the main breakdown product, mono(2-ethylhexyl)phthalate, or MEHP. It is also unknown whether DEHP is the chemical uniquely responsible for causing the negative symptoms seen in animal studies, or whether a breakdown product, such as MEHP, is responsible. This could be important since in primates and humans, for example, MEHP is formed at much lower levels within the digestive system than is the case in rats and mice. It also relates back to the pathway of exposure, in that humans receiving an exposure to phthalates through, say, a feeding tube would subject the DEHP to different metabolic processing than they would to DEHP injected during, say, a dialysis procedure.

D. Different Cancer-causation Mechanisms

Besides the direct observation of tumor growth, there are other methods of testing a chemical for cancer-causing potential. One physiological process that scientists monitor to gauge the cancer-causing potential of a chemical is called "peroxisome proliferation." In peroxisome proliferation studies, scientists look for evidence that certain cell bodies called peroxisomes have developed at abnormally high levels in liver cells or other suspected sites of cancer formation. But the peroxisome proliferation ability of different chemicals differs among different animal species, and it is uncertain whether peroxisome proliferation is truly an indicator of cancer-causing potential. The Syrian hamster, for example, is four times less likely to display peroxisome proliferation when given the same dose of a known peroxisome proliferator as a rat or mouse. Dogs and rhesus monkeys are even less likely to experience peroxisome proliferation when given chemicals known to cause

peroxisome proliferation in rats and mice. Huber, et al. point out that: "The greater sensitivity of the rat to peroxisome proliferators such as DEHP suggests that human risk calculations based exclusively on rat data and dose might lead to an overestimation of the actual threat." Huber, et al. also observe that: "These results emphasize that substances stronger than DEHP by several orders of magnitude at very high doses, far above those found in risk groups of DEHP exposure, are required to induce the phenomenon of peroxisome proliferation in primates, probably including humans." Most recently, the United Nation's International Agency for Research on Cancer changed the classification of DEHP from a "possible" human carcinogen to "Cannot be classified as to its carcinogenicity in humans."

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E. The Dose Makes the Poison

The magnitude of the final absorbed dose is critical. The first law of toxicology is that "the dose makes the poison." With the exception of extracorporeal oxygenation, a life-saving procedure used on infants, human exposures to phthalates are generally orders of magnitude lower than the doses shown to cause even minor illness in experimental animal subjects.

Much of the concern over phthalates stems from the level of "conservatism" that different analysts or regulators believe is the most valid metric of safety. Most regulatory agencies in the U.S. hold that a chemical exposure is potentially dangerous unless it is 100 times lower than the level at which experimental animals show no observed adverse effects. Others hold that such conservatism is inherently arbitrary.

As Table 4 shows, even in the liver, the body organ most susceptible to chemical impacts, and even for highly exposed people, the DEHP dose rate is at least eight fold below the "no effect" threshold for liver enlargement or other signals of possible cancer-causation. And the dose rate is over 16 times less than the Low Observed Effect Level seen to actually produce liver tumors or other cancer indicators (peroxisome proliferation) in animal tests. For more moderately exposed people, exposures are thousands of times lower than the Low Observed Effect Levels seen to produce liver tumors or other possible cancer indicators.

With the exception of extracorporeal oxygenation, a life-saving procedure used on infants, human exposures to phthalates are generally orders of magnitude lower than the doses shown to cause even minor illness in experimental animal subjects.

Table 4: Worst-case Exposures of General Public and Hemodialysis Patients to DEHP (as Compared to Doses Shown to Induce Tumors or Other Possible Cancer-indicators Such as Peroxisome Proliferation in Rats and Mice)

Effect of DEHP	Species	Impact Level	Dose in mg/kg-b.w./d	Safety factor for people with typical exposure to DEHP[a]	Safety factor for Hemodialysis patient exposure[b]
Peroxisome Proliferation and liver enlargement	Rat	LOEL	50	1670	16
Peroxisome Proliferation and liver enlargement	Rat	NOEL	25	830	8
Tumors	Rat	LOEL	400	10,000	97
Tumors	Rat	NOEL	50	1,670	16

Tumors	Mouse	LOEL	300	10,000	97
Tumors	Mouse	NOEL	100	3,300	32

Source: Wolfgang Huber et al., "Hepatocarcinogenic Potential of Di(2-ethylhexyl)phthalate in Rodents and its Implications on Human Risk," *Critical Reviews in Toxicology*, vol. 26, issue 4 (June 1996), Table 52, p. 460.

Notes:

a) These values actually have an additional 30X safety factor built into the calculation. Most government agencies consider a substance "safe" based on how many levels of 10X safety factors are between the human exposure and the experimental dose shown to cause no observable effect. The values in this column are multiples of the exposures considered safe, thus, are actually 30 times higher in reality than is reflected here.

b) This actually has an additional 3X safety factor built into the basic calculation.

Part 5

Comparing Animal and Human Exposures

A. Comparing Human Exposures to Doses Causing Whole-Body Illness in Animals

1. DEHP

Based on standard toxicology testing, DEHP shows very low acute toxicity, that is, low toxicity from a single high dose. The "benchmark" measure of toxicity is called the LD_{50}, the dose at which 50 percent of a test population dies upon exposure to a given substance. The LD_{50} for phthalates administered to rats by injection, for example, is equivalent to 0.0002 percent of body weight. By comparison, the LD_{50} for feeding caffeine to a rat is also about 0.0002 percent of body weight. For rabbits and mice, the LD_{50} for DEHP injection was 0.034 percent of body weight in DEHP, while in guinea pigs, the LD_{50} required 0.026 percent of body weight in DEHP.

Dogs are clearly less sensitive to DEHP toxicity. Dogs fed 0.05 percent of their body weight of DEHP for 14 weeks showed only slight weight loss.

Another benchmark indicator of toxicity is called the Low Observed Effect Level, or LOEL. This is the level at which negative effects are first seen. In rats, the LOEL was observed at a dose of 0.02 percent body weight per day, administered over two years.

As Table 3 shows, newborns undergoing a drastic and rare procedure called extracorporeal blood oxygenation can receive a short-term dose of 0.014 percent of body weight. The next most-highly-exposed humans, infants receiving a short-term dose of up to 0.00019 percent of their body weight while receiving concentrated blood platelets, receive a dose over a hundred times lower than the lowest dose level shown to cause negative effects in rats when administered over most of the animal's lifetime.

A third indicator of toxicity is called the No Observed Effect Level, or NOEL. This is the highest dose that still produces no signs of toxicity. For rats, the NOEL for DEHP was 0.006 percent of their body weight per day, administered over two years. In addition, there was no reduction in the average life span of rats or mice fed up to 10 times the NOEL level, or 0.06 percent of their body weight in DEHP per day, administered through their normal diet. This is a lifetime exposure to 4.3 times more DEHP than the most highly exposed human would be exposed to for only a few days.

DEHP is a very minor skin or eye irritant when administered topically, though when injected directly into the skin the evidence for irritation is contradictory. For humans in occupational settings, inhalation of mixed phthalate levels at concentrations 1 and 60 milligrams of phthalate per cubic meter of air were observed to cause irritation to the nose and pharynx. After long exposure to such an air concentration (two years), there is some evidence that phthalates cause problems with the neuromuscular system, mostly in the legs. However, the only studies suggesting this effect had methodological problems that cast doubt on the validity of that finding.

DEHP has tested negative for the ability to cause genetic destruction or alteration in a number of test systems based on microbes, mammalian cells, or mammalian cell components. Finally, DEHP does not seem to trigger allergic responses in humans.

Table 5 shows how the top three human exposures to DEHP compare to the NOEL level of systemic toxicity developed from toxicological testing. Note that the very highest human exposure, for infants receiving extracorporeal oxygenation (a short-term, life-saving procedure) is lower than the LOEL for total-body impacts in the rat, while the exposure length is vastly shorter: days to weeks for humans, but nearly the total lifespan for rats.

Table 5: Maximum Human DEHP Exposure Compared to LOEL or NOEL Shown to Cause Systemic Harm

Exposure to DEHP	Worst-case exposure in mg/kg-b.w./dy	Source
DEHP via extracorporeal oxygenation in infants	42-140	Huber et al., p 370
DEHP via platelet and whole blood transfusion in infants	2.1-27.5	Huber et al, p. 370
Systemic toxicity from DEHP	Dose in mg/kg-b.w./dy	Source
LOEL Rat (male)	200	Huber, et al., p. 438
NOEL Rat (male)	60	Huber, et al., p. 438

Source: Wolfgang Huber et al., "Hepatocarcinogenic Potential of Di(2-ethylhexyl)phthalate in Rodents and its Implications on Human Risk," *Critical Reviews in Toxicology*, vol. 26, issue 4 (June 1996), pp. 370, 438.

2. DINP

Even by comparison to DEHP, which is itself low in toxicity, the toxicity of DINP is low. No adverse effects are seen in rats at doses below 0.009 percent of body weight per day for male rats, 0.011 percent of body weight per day for female rats, and 0.05 percent of body weight per day for marmoset monkeys. DINP tested negative in experiments measuring the ability to mutate genes, including the Ames test, test systems using Chinese hamster ovary cells and rat bone marrow. DINP also tested negative in tests for chromosomal damage, tests for the ability to activate DNA activity, and others.

Based on standard toxicology testing, DEHP shows very low acute toxicity, that is, low

toxicity from a single high dose.

Table 6 shows how the worst-case human exposures to DINP compare to the NOEL level for systemic toxicity developed from animal testing. Note that exposure to DINP is about 160 times lower than the lifelong dose shown to cause no negative health effects in male rats.

Table 6: Maximum Human DINP Exposure Compared to NOEL or LOEL Shown to Cause Systemic Harm		
Exposure to DINP	Worst-case exposure in mg/kg-b.w./dy	Source
DINP via toy mouthing (3-12 month olds)	0.0943	CPSC, table 4.
DINP via toy mouthing (13-26 month olds)	0.0076	CPSC, table 4
Systemic toxicity from DINP	Dose in mg/kg-b.w./dy	Source
NOEL Rat (male)	88	Koop, Juberg et al., p. 22
NOEL Rat (female)	109	Koop, Juberg et al., p. 22
NOEL Mice (male)	276	Koop, Juberg et al., p. 22
NOEL Mice (female)	112	Koop, Juberg et al., p. 22
NOEL Marmoset	500	CERHR, p. 3

Sources: Wolfgang Huber et al., "Hepatocarcinogenic Potential of Di(2-ethylhexyl)phthalate in Rodents and its Implications on Human Risk," *Critical Reviews in Toxicology*, vol. 26, issue 4 (June 1996); C. Everett Koop, Daland R. Juberg et al., *A Scientific Evaluation of Health Effects of Two Plasticizers Used in Medical Devices and Toys: A Report from the American Council on Science and Health* (Washington, D.C.: American Council on Science and Health, June 1999) (www.medscape.com); Michael A. Babich, *The Risk of Chronic Toxicity Associated with Exposure to Diisononyl Phthalate (DINP) in Children's Products*, (Washington, D.C.: United States Consumer Product Safety Commission, December 1998) (http://www.cpsc.gov/phth/dinp.html); and National Toxicology Program, Center for Evaluation of Risks to Human Reproduction, National Institute of Environmental Health Sciences, "Draft DINP Monograph, Section 5," December 1, 1999 (http://cerhr.niehs.nih.gov/news/ Sec5_DINP.htm).

B. Comparing Human Exposures to Doses Causing Liver or Kidney Damage in Animals

1. DEHP

A recent study validated the findings of the NTP report mentioned earlier. The study by R.M. David et al. exposed rats and mice to the following levels of DEHP for 104 weeks, administering:

- 0.0006, 0.0029, 0.0147, or 0.0789 percent of body weight per day for male rats;

- 0.0007, 0.0036, 0.0182, or 0.0938 percent of body weight per day for female rats;
- 0.0019, 0.0099, 0.0292, or 0.1266 percent of body weight per day for male mice; and
- 0.0024, 0.0177, 0.0254, or 0.1458 percent of body weight per day for female mice.

At the end of the trials, the high-dose animals showed signs of liver enlargement; evidence of cancer-related biochemical effects; and formation of liver tumors at a higher rate than did the non-exposed or lower-dose test animals. The tumors stopped growing when exposure to DEHP was removed. In a separate study of DEHP toxicity in dogs, no liver toxicity was observed at DEHP doses of up to 0.023 percent of body weight administered over three weeks.

Table 7 shows how the top two human exposures to DEHP compare to the NOEL or LOEL level of liver or kidney toxicity developed from toxicological testing. Note that the short-term highest human exposure is half that of the lowest lifelong dose shown to cause low-level induction of liver tumors in rats.

Table 7: Maximum Human DEHP Exposure Compared to NOEL or LOEL for Damage to Liver or Kidneys

Exposure to DEHP	Worst-case exposure in mg/kg-b.w./dy	Source
DEHP via extracorporeal oxygenation in infants	42-140	Huber et al., p 370
DEHP via platelet and whole blood transfusion in infants	2.1-27.5	Huber et al, p. 370

Liver / kidney toxicity from DEHP	Dose in mg/kg-b.w./dy	Source
NOEL Liver tumors (Rat)	50-100	Huber, p. 443
LOEL Liver tumors (Rat)	300	Huber, p. 443
NOEL Liver impacts (Mouse)	19-24	Koop, Juberg et al., p. 7
NOEL (Dogs)	187-232	Koop, Juberg et al., p. 10

Sources: Wolfgang Huber et al., "Hepatocarcinogenic Potential of Di(2-ethylhexyl)phthalate in Rodents and its Implications on Human Risk," *Critical Reviews in Toxicology*, vol. 26, issue 4 (June 1996); C. Everett Koop, Daland R. Juberg et al., *A Scientific Evaluation of Health Effects of Two Plasticizers Used in Medical Devices and Toys: A Report from the American Council on Science and Health*, (Washington D.C.: American Council on Science and Health, June 1999) (www.medscape.com).

2. DINP

In a 1999 study, DINP was administered to F344 rats (one purebred strain of rats commonly used in laboratory research) and B6C3F1 mice (one purebred strain of mice commonly used in laboratory research) for up to two years at doses of:

- 0.0029, 0.0088, 0.0359, and 0.0733 percent of body weight per day for male rats;

- 0.0036, 0.0109, 0.0442, 0.0885 percent of body weight per day for female rats;
- 0.0090, 0.0276, 0.0742, 0.1560 percent of body weight per day for male mice;
- 0.0112, 0.0336, 0.0910, and 0.1888 percent of body weight per day for female mice.

In rats, higher dose levels produced liver and kidney toxicity and enlargement as well as an increase in liver tumors in males and females, an increase in cancerous kidney tumors in males, and an increase in a disease nearly unique to the particular strain of rats used in the study, mononuclear cell leukemia. Much of the liver and kidney enlargement was reversible, with the organs returning to normal size after cessation of exposure. In mice, doses above the no-effect level produced similar liver and kidney toxicity, but no mononuclear cell leukemia or kidney cancer. Though tests in rats show kidney tumor formation at feedings of a diet consisting of 1.2 percent DINP, the mechanism of tumor formation was found not relevant to humans by the U.S. Environmental Protection Agency (EPA) and the Presidential/Congressional Commission on Risk Assessment and Risk Management.

Though tests in rats show kidney tumor formation at feedings of a diet consisting of 1.2 percent DINP, the mechanism of tumor formation was found not relevant to humans by the U.S. Environmental Protection Agency (EPA) and the Presidential/Congressional Commission on Risk Assessment and Risk Management.

Tests in marmoset monkeys with doses of 0.01, 0.05, and 0.25 percent of body weight per day of DINP failed to produce tumors, other signs of cancer-causing ability, or other damage to liver tissue, with a conservative NOEL level of 0.05 percent of body weight per day being accepted in the literature. Tests in macaque monkeys treated with 0.05 percent of body weight per day of DINP showed no liver damage.

Table 8 shows how the top two human exposures to DINP compare to the NOEL level of liver or kidney toxicity developed from toxicological testing. Note that the highest short-term human exposure is over 160 times lower than the lifelong No Observed Effect Level dose observed in rats, and about 5,000 times lower than the No Observed Effect Level dose in marmoset monkeys.

Table 8: Maximum Human DINP Exposure Compared to NOEL or LOEL for Damage to Liver or Kidneys

Exposure to DINP	Worst-case exposure in mg/kg-b.w./dy	Source
DINP via toy mouthing (3-12 month olds)	0.0943	CPSC, table 4
DINP via toy mouthing (13-26 month olds)	0.0076	CPSC, table 4
Liver / kidney toxicity from DINP	Dose in mg/kg-b.w./dy	Source
LOEL Rat (male)	152	CPSC, (Lington) p. 5
LOEL Rat (male)	88	CPSC, (Moore) p. 5
NOEL marmoset	500	Koop, Juberg et al., p. 23
NOEL Rat (female)	15	CPSC, p. 5
NOEL Mouse (male)	276	Koop, Juberg et al., p. 22
NOEL Mouse (female)	15	Huber, et al., p. 438

Sources: Wolfgang Huber et al., "Hepatocarcinogenic Potential of Di(2-ethylhexyl)phthalate in Rodents and its Implications on Human Risk," *Critical Reviews in Toxicology*, vol. 26, issue 4 (June 1996); C. Everett Koop, Daland R. Juberg et al., *A Scientific Evaluation of Health Effects of Two Plasticizers Used in Medical Devices and Toys: A Report from the American Council on Science and Health* (Washington, D.C.: American Council on Science and Health, June 1999) (www.medscape.com); and Michael A. Babich, *The Risk of Chronic Toxicity Associated with Exposure to Diisononyl Phthalate (DINP) in Children's Products*, (Washington, D.C.: United States Consumer Product Safety Commission, December 1998) (http://www.cpsc.gov/ phth/dinp.html).

C. Comparing Human Exposures to Doses Causing Heart or Lung Damage in Animals

1. DEHP

Exposed to high levels of DEHP, laboratory rats and mice can experience significant impacts to the heart and lungs, but these effects depend more on the substance that the DEHP is dissolved in than on the DEHP itself. For example, when DEHP was dissolved in an oil-based solution, toxic impacts to the lungs were noted, but when the DEHP was dissolved in an aqueous solution, toxic lung effects were not observed, even if the DEHP concentration was ten times higher. The oil-based solution alone, on the other hand, caused no ill effects, but somehow made the DEHP's impact stronger. When DEHP was administered by mixing it in with donor blood, toxic effects were seen in rats and mice, with an LD_{50} at 0.02 percent of body weight per day, and an LD_{100} at 0.04 percent of body weight per day.

The level shown to cause only low-level impacts to the heart or lungs of experimental animal subjects was still six-fold higher than the maximum DEHP dose observed in an adult during a blood transfusion. *Worst-case* calculations suggest that some newborns may receive certain life-saving medical procedures that expose them to short-term doses of DEHP that approach the lifelong LOEL level for causing damage to the heart and lungs in experimental animal subjects.

Table 9 shows how the worst-case human exposures to DEHP compare to the NOEL level for heart and lung toxicity developed from animal testing. Note that even the worst exposed human receives four times less DEHP than the lowest dose seen to cause lung toxicity in the rat, though the human dose is for a far smaller fraction of the lifespan than is the case for the rat exposures.

Table 9: Maximum Human DEHP Exposure Compared to NOEL or LOEL for Heart / Lung Damage

Exposure to DEHP	Worst-case exposure in mg/kg-b.w./dy	Source
DEHP via extracorporeal oxygenation in infants	42-140	Huber et al., p. 370
DEHP via platelet and whole blood transfusion in infants	2.1-27.5	Huber et al., p. 370
Heart / lung toxicity from DEHP	Dose in mg/kg-b.w./dy	Source
LOEL lung toxicity (rat)	215	Koop, Juberg et al., p. 10
NOEL (rat)	155	Koop, Juberg et al., p. 10

Source: Wolfgang Huber et al., "Hepatocarcinogenic Potential of Di(2-ethylhexyl)phthalate in Rodents and its Implications on Human Risk," *Critical Reviews in Toxicology*, vol. 26, issue 4 (June 1996).

2. DINP

Impacts of DINP on the heart and lungs have not been studied specifically, though chronic studies (previously discussed) consider the heart and lungs as potential sites of damage. In those studies, no effects to the heart or lungs were noted.

D. Comparing Human Exposures to Doses Causing Impact to the Endocrine Organs or Hormone Systems of Animals

1. DEHP

Supplementing the diet of rats with DEHP to levels from 0.05 percent of body weight per day to 0.1 percent of body weight per day produced decreases in one thyroid hormone (thyroxine) but not in T3, a different thyroid hormone. The decrease cannot be explained, but it seems to be common with other compounds found capable of promoting tumor growth. DEHP has been tested for estrogen-like effects in both animal and non-animal test systems, but has shown no estrogenic impacts in any test system. At 0.05 percent of body weight per day, the lowest dose shown to have long-term thyroid impacts in rats is over three times higher than the maximum human exposure, which is short-term in nature.

2. DINP

DINP has been tested for estrogen-like effects in both animal and non-animal test systems but has shown no estrogenic impacts in any test system. Thyroid impacts of DINP have not been studied.

E. Comparing Human Exposures to Doses Damaging the Reproductive Organs, or Causing Fetal or Maternal Toxicity in Animals

1. DEHP

Studies show that rats fed high doses of DEHP can experience reversible damage to the testes, including reduction in testicular size, decreased sperm production, and decreased zinc concentrations. Within 12 to 20 days after cessation of the DEHP exposure, this damage is reversed, returning the testes to normal. Less damage was seen to the ovaries from similar doses. At doses above 0.0750 percent of body weight per day, reduction in testicular size was apparent in rats, though depressed sperm count was seen at 0.05 percent of body weight per day, testicular zinc depletion was seen at 0.015 percent of body weight per day, and changes in cell shape were observed at exposures of 0.01 percent of body weight per day. But studies suggest that the damage is caused by MEHP, a breakdown product of DEHP that forms mainly after ingestion and much less after injection. Further, the effects were species specific, as are other observed DEHP effects, though the species sensitivity to reproductive-organ damage differs from that for, say, liver damage. Guinea pigs were more likely to experience DEHP-related testicular toxicity than were rats. Results for mice are inconsistent, while marmoset testes were unaffected after two weeks of treatment with either 0.2 percent of body weight per day orally, or 0.100 percent of body weight per day by direct injection into the body cavity.

Table 10 shows how the worst-case human exposures to DEHP compare to the NOEL level for reproductive or developmental toxicity developed from animal testing. Note that even the worst exposed human receives 1.5 times less DEHP than the lowest dose seen to cause reproductive toxicity in the rat, though the human dose is for a far smaller fraction (and a non-pregnant one) of the life span than is the case for the rat exposures.

Table 10: Maximum Human DEHP Exposure Compared to NOEL or LOEL for Reproductive

Toxicity		
Exposure to DEHP	Worst-case exposure in mg/kg-b.w./dy	Source
DEHP via extracorporeal oxygenation in infants	42-140	Huber et al., p. 370
DEHP via platelet and whole blood transfusion in infants	2.1-27.5	Huber et al., p. 370
Reproductive toxicity from DEHP	Dose in mg/kg-b.w./dy	Source
NOEL testicular toxicity (marmoset) (oral)	2000	Koop, Juberg et al., p. 9
NOEL testicular toxicity (marmoset) (injected)	1000	Koop, Juberg et al., p. 9
NOEL teratogenicity / fetotoxicity (rat)	357	Huber et al., p. 438
LOEL teratogenicity / fetotoxicity (rat)	666	Huber et al., p. 438
NOEL teratogenicity / fetotoxicity (mouse)	44	Huber et al., p. 438
LOEL teratogenicity / fetotoxicity (mouse)	91	Koop, Juberg et al., p. 9
NOEL reproductive toxicity (rat)	10	CERHR, p. 12

Sources: Wolfgang Huber et al., "Hepatocarcinogenic Potential of Di(2-ethylhexyl)phthalate in Rodents and its Implications on Human Risk," *Critical Reviews in Toxicology*, vol. 26, issue 4 (June 1996); C. Everett Koop, Daland R. Juberg et al., *A Scientific Evaluation of Health Effects of Two Plasticizers Used in Medical Devices and Toys: A Report from the American Council on Science and Health* (Washington, D.C.: American Council on Science and Health, June 1999) (www.medscape.com); and National Toxicology Program, Center for Evaluation of Risks to Human Reproduction, National Institute of Environmental Health Sciences, "Draft DINP Monograph, Section 5," December 1, 1999 (http://cerhr.niehs.nih.gov/news/Sec5_DINP.htm).

2. DINP

Doses of DINP at up to 0.0668 percent of body weight per day in Sprague-Dawley rats (another purebred strain of rats frequently used in toxicology studies) resulted in no adverse effects on reproduction, including fertility, testicular effects, or transgenerational effects.

DINP has also been examined for impacts on developing embryos. In a study where DINP was fed to pregnant Wistar rats (yet another purebred strain of rats used in toxicology testing) at doses of 0.004, 0.02, or 0.1 percent of body weight per day, maternal toxicity and some developmental effects were seen at the high dose, but not the lower. A subsequent study used a different strain of pregnant rats, fed DINP doses of 0.0001, 0.01, 0.05, and 0.1 percent of body weight per day, to examine impacts on pregnant females and developing embryos. Mild maternal and developmental effects were observed at the highest dose level, but no adverse effects were noted even at the second-highest DINP dose of 0.05 percent of body weight per day.

Table 11 shows how the worst-case human exposures to DINP compare to the NOEL level for reproductive or developmental toxicity developed from animal testing. Note that even the worst exposed human receives a short-term exposure to nearly 77,000 times less DINP than the lowest dose seen to cause reproductive toxicity with a lifelong exposure in the rat.

Table 11: Maximum Human DINP Exposure Compared to NOEL or LOEL for Reproductive Toxicity

Exposure to DINP	Worst-case exposure in mg/kg-b.w./dy	Source
DINP via toy mouthing (3-12 month olds)	0.0943	CPSC, table 4
DINP via toy mouthing (13-26 month olds)	0.0076	CPSC, table 4
Reproductive toxicity from DINP	Dose in mg/kg-b.w./dy	Source
NOEL ovarian tox (rat/mouse)	885	CERHR, p. 7
NOEL teratogenicity / fetotoxicity (rat)	200	CERHR, p. 4
LOEL teratogenicity / fetotoxicity (rat)	1000	CERHR, p. 4
NOEL developmental (rat)	10	CERHR, p. 12
LOEL developmental (rat)	150	CERHR p. 6
NOEL maternal toxicity (rat)	200	CERHR, p. 6

Sources: Michael A. Babich, *The Risk of Chronic Toxicity Associated with Exposure to Diisononyl Phthalate (DINP) in Children's Products* (Washington, D.C.: United States Consumer Product Safety Commission, December 1998) (http://www.cpsc.gov/phth/dinp.html); and National Toxicology Program, Center for Evaluation of Risks to Human Reproduction, National Institute of Environmental Health Sciences, "Draft DINP Monograph, Section 5," December 1, 1999 (http://cerhr.niehs.nih.gov/news/Sec5_DINP.htm)

F. Benefits: the Other Side of Risk

In the case of medical devices, people are receiving exposures to DEHP as a byproduct of beneficial medical treatment. If one is concerned about the risk posed by DEHP exposure, a holistic view of risk would also have to consider the alternatives, and the prospect for trading one risk (the risk of DEHP exposure) for another (such as the risk of using an inferior medical device). As the ACSH study points out, PVC medical products convey many benefits that alternative products do not. Phthalate-softened plastics offer benefits such as clarity, strength, flexibility, kink resistance, compatibility with intravenous solutions, and cost-effectiveness. Koop, Juberg et al., also point out that DEHP has a very important preservative effect on stored blood, reportedly doubling the shelf-life of whole blood and increasing the stability of red blood cells both when stored and when being transfused into patients. Another benefit of PVC intravenous bags is their self-collapsing nature, which eliminates the need to feed air into the bag in order to get the liquid out. This reduces the need for air sterilization equipment that is not only costly but can allow an additional chance of infection during drug or blood administration.

The number of Americans currently receiving such benefits is substantial: In 1996, 31.5 million outpatient surgeries and 40.3 inpatient surgeries were performed. If phthalate-softened PVC products are used in only half of all surgeries, nearly one-third of the population derives a health benefit from them in any given year.

Whole blood stored in a PVC bag remains viable for 42 days, compared to only 21 days for other containers. According to America's Blood Centers, more than 23 million blood components are made from about 14 million whole blood donations (stored in PVC bags) yearly. And that blood supply is fully utilized. Table 12 gives some examples of blood product use.

In addition to blood, surgical procedures frequently require the administration of saline and medicinal solutions via intravenous delivery, which is both safer and more cost-effective when administered via PVC bags as compared to alternatives.

Another use of vinyl where transparency and kink-resistance is important is in the use of tubing used for long-term chronic oxygen therapy. For the nearly 800,000 Americans tethered to oxygen tanks or outlets in their homes, flexible PVC tubing provides a considerable benefit in terms of lifestyle improvement.

Table 12: Examples of Blood Product Uses and Quantities	
Uses	Quantity per use
Automobile accident	50 units of blood
Bone marrow transplant	20 units of blood 120 units of platelets
Organ transplant	40 units of blood 30 units of platelets 20 bags of cryoprecipitate 25 units of fresh frozen plasma
Burn	20 units of platelets
Heart Surgery	6 units of blood 6 units of platelets

Source: America's Blood Centers web site (http://www.americasblood.org/).

Part 6

Summary

People are increasingly concerned about the safety of their food, water, consumer, and medical products. Groups such as Greenpeace and Health Care Without Harm have suggested that phthalates, chemicals used to soften normally-rigid polyvinyl chloride plastics, pose a threat to human health via exposures through medical and consumer products, and should be banned.

Yet as several research groups have shown, few humans, if any, are exposed—even on a short-term basis—to a dose of phthalates shown to cause even minor harm in animal tests when administered over a lifetime. Indeed, with the exception of short-term, life-saving medical procedures, safety margins for typical human exposure to phthalates are well over 1000, while phthalates provide benefits which some have suggested outweigh the incremental risk posed by exposure to them. With few exceptions, human exposures stemming from medical procedures are well below those shown to cause harm in animal tests:

- While a lifetime DEHP dose of 200 milligrams per kilogram of body weight per day can cause low amounts of systemic illness in rats, people at the high end of DEHP exposure (via dialysis) get a short term dose that is 28 times less.

- While a lifetime DEHP dose of 50 milligrams per kilogram of body weight per day can cause low level cancerous changes and liver enlargement in rats, people at the high end of DEHP exposure (via dialysis) get a short term dose that is seven times less.
- While a lifetime DEHP dose of 400 milligrams per kilogram of body weight per day can cause liver tumors in rats, people at the high end of DEHP exposure (via dialysis) get a short term dose that is 56 times less.

• Even the maximally exposed human being, a child receiving a life-saving treatment called extracorporeal blood oxygenation is exposed—for only a short time—to a dose which that is 70 percent of the lifetime dose shown to cause only a low level of observed health hazard in rats.

For DINP, the situation is similar: while animal tests suggest that high dosages, administered over long time periods can cause various types of harm, humans are exposed to doses that are far lower, and for far shorter periods of time.

- While a lifetime dose of 88 milligrams per kilogram of body weight per day led to only a low level of observed adverse health impacts to male rats, maximally exposed humans are exposed to a dose which is over 6,000 times less, generally, for less than two years.

About the Author

Dr. Kenneth Green is Director of the Environmental Program at Reason Public Policy Institute. Dr. Green has published peer-reviewed policy studies on climate change, air quality and environmental risk including: *Seeking Safety in a Dangerous World, A Plain English Guide to the Science of Climate Change, Rethinking EPA's Proposed Ozone and Particulate Standards, Estimating Fatalities Induced by Economic Impacts of EPA's proposed Ozone and Particulate Standards (co-authored), Looking Beyond ECO, Defending Automobility,* and *Checking Up on Smog Check*. Green received his doctorate in environmental science and engineering (D.Env.) from UCLA in 1994, joined Reason Public Policy Institute soon after, and now works from his home-office in Central Texas.

Other Reason Public Policy Institute Studies

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1996.

Endnotes

1. www.greenpeacecanada.org/toys/table2.html; Healthcare Without Harm Media Advisory, February 23, 1999; and Charlie Cray, "Experimenting on Children," *Rachel's Environment & Health Weekly*, No. 603, June 1998 (www.envirotrust.com/RachelsPVC.html).
2. Joel Tickner, et al., "*The Use of Di-2-Ethylhexyl Phthalate in PVC Medical Devices: Exposure, Toxicity, and Alternatives*," (Lowell, Massachusetts: Lowell Center for Sustainable Production, University of Massachusetts, June, 1999).
3. C. Everett Koop, Daland R. Juberg et al., *A Scientific Evaluation of Health Effects of Two Plasticizers Used in Medical Devices and Toys: A Report from the American Council on Science and Health* (Washington, D.C.: American Council on Science and Health, June 1999) (www.medscape.com); Wolfgang Huber et al., "Hepatocarcinogenic Potential of Di(2-ethylhexyl)phthalate in Rodents and its Implications on Human Risk," *Critical Reviews in Toxicology*, vol. 26, issue 4 (June 1996); Babich, *The Risk of Chronic Toxicity Associated with Exposure to Diisononyl Phthalate (DINP) in Children's Products* (Washington, D.C.: United States Consumer Product Safety Commission, December 1998) (http://www. cpsc.gov/phth/dinp.html).
4. Huber et al., "Hepatocarcinogenic Potential of Di(2-ethylhexyl)phthalate in Rodents and its Implications on Human Risk."
5. Babich, *The Risk of Chronic Toxicity Associated with Exposure to Diisononyl Phthalate (DINP) in Children's Products*.
6. Specifically, the Consumer Product Safety Commission recommended convening a Chronic Hazard Advisory Panel to study issues relating to chronic toxicity and cancer, especially the cancer risk; conducting a more extensive observational study of children's mouthing behavior; working toward the development of a laboratory test method that more accurately estimates phthalate release from products; and continuing testing of children's products for the presence and release of DINP. See Babich, *The Risk of Chronic Toxicity Associated with Exposure to Diisononyl Phthalate (DINP) in Children's Products*.
7. Koop, Juberg, et al., *A Scientific Evaluation of Health Effects of Two Plasticizers Used in Medical Devices and Toys*, p. 2.
8. United Nations International Agency for Research on Cancer, IARC, (http://193.51.164.11/past&future/evaltab77.html) and (http://193.51.164.11/htdocs/announcements/vol77.htm). Explaining the reclassification, an IARC monograph states: "In making its overall evaluation of the possible carcinogenicity to humans of DEHP, the working group took into consideration that (a) DEHP produces liver tumours in rats and mice by a non-DNA-reactive mechanism involving peroxisome proliferation; (b) peroxisome proliferation and hepatocellular proliferation have been demonstrated under the conditions of the carcinogenicity studies of DEHP in mice and rats; and (c) peroxisome proliferation has not been documented in human hepatocyte cultures exposed to DEHP nor in the livers of exposed non-human primates. Therefore, the mechanism by which DEHP increases the incidence of hepatocellular tumours in rats and mice is not relevant to humans.
9. The most relevant statute guiding the CPSC in its decision making is the Federal Hazardous Substances Act, or FHSA. The FHSA does not provide for pre-market registration or approval of products, nor does it require manufacturers to perform any specific tests to assess the potential for chronic hazards. This places the responsibility on manufacturers to ensure either that their products are not "hazardous substances" as defined by the FHSA, or, if they are, that they are labeled as required under the FHSA. The exception is for children's products, which are banned if they include a hazardous substance. The FHSA only defines what is harmful, not what is "safe" or beneficial. Therefore, the CPSC is limited to considering only risks, not benefits. (By correspondence with Michael Babich, United States Consumer Product Safety Commission).
10. Aaron Wildavky, *Searching for Safety* (New Brunswick: Transaction Publishers, 1991). For a more concise discussion of how certainty and uncertainty constrain risk management policy, see Kenneth Green, *Seeking Safety in a Dangerous World: a Risk-Reduction Framework for Policymakers*, Policy Study No. 261 (Los Angeles: Reason Public Policy Institute, August 1999).
11. National Toxicology Program, Center for Evaluation of Risks to Human Reproduction, National Institute of Environmental Health Sciences, "Seven Phthalates," 1999 (http://cerhr.niehs.nih.gov/CERHR

chems/7phthalates.html).

12. Huber et al., "Hepatocarcinogenic Potential of Di(2-ethylhexyl)phthalate in Rodents and its Implications on Human Risk," p. 367.
13. David G. Pegg, "Disposition of Di-2-ethylhexyl Phthalate Following Inhalation and Peroral Exposure in Rats," General Motors Research Laboratories, available from General Motors Research Laboratories, or from author upon request.
14. National Toxicology Program, Center for Evaluation of Risks to Human Reproduction, National Institute of Environmental Health Sciences, "Draft DINP Monograph, Section 5," December 1, 1999 (http://cerhr.niehs.nih. gov/news /Sec5_DINP.htm).
15. B. Roth, et al., "Di-(2-ethylhexyl)-phthalate as Plasticizer in PVC Respiratory Tubing Systems: Indications of Hazardous Effects on Pulmonary Function in Mechanically Ventilated, Preterm Infants," *European Journal of Pediatrics*, vol. 147 (1988), pp. 41-46.
16. No specific data on DEHP ingestion during medical treatment is available. However, rates of ingestion based on mouthing of toys are probably comparable, if scaled appropriately with the length of exposure.
17. Huber et al., "Hepatocarcinogenic Potential of Di(2-ethylhexyl)phthalate in Rodents and its Implications on Human Risk," p. 379.
18. [12] Ibid.
19. R.S. Harris et al., "Chronic Oral Toxicity of 2-ethylhexyl-phthalate in Rats and Dogs," *Archives of Industrial Health*, vol. 13 (1956), pp. 259-264.
20. Huber et al., "Hepatocarcinogenic Potential of Di(2-ethylhexyl)phthalate in Rodents and its Implications on Human Risk," p. 440.
21. Ibid., p. 391.
22. Ibid., p. 379.
23. Ibid., p. 376, 392.
24. Ibid., p. 425.
25. Ibid., p. 415.
26. George M. Gray, *Key Issues in Environmental Risk Comparisons: Removing Distortions and Insuring Fairness*, Policy Study No. 205 (Los Angeles: Reason Public Policy Institute, May 1996).
27. Huber et al., "Hepatocarcinogenic Potential of Di(2-ethylhexyl)phthalate in Rodents and its Implications on Human Risk," p. 461.
28. Martha Windholz, Ed., *The Merck Index, An Encyclopedia of Chemicals and Drugs, Ninth Edition* (Rahway, N.J.: Merck & Co., Inc., 1976).
29. Sometimes also called the Lowest Observed Effect Level (LOEL) or the Lowest Observed Adverse Effect Level, (LOAEL).
30. Equivalent to ingesting 0.48 ounces each day for 2 years, for a 150 pound person.
31. Sometimes also called the No Observed Effect Level (NOEL) or the No Observed Adverse Effect Level, (NOAEL).
32. Equivalent to ingesting 0.14 ounces per day for 70 years, for a 150 pound human.
33. Equivalent to ingesting 1.44 ounces per day for 70 years, for a 150 pound human.
34. Huber et al., "Hepatocarcinogenic Potential of Di(2-ethylhexyl)phthalate in Rodents and its Implications on Human Risk.," p. 442.
35. Koop, Juberg, et al., "A Scientific Evaluation of Health Effects of Two Plasticizers Used in Medical Devices and Toys," p. 8.
36. Huber et al., "Hepatocarcinogenic Potential of Di(2-ethylhexyl)phthalate in Rodents and its Implications on Human Risk," p. 438.
37. LOEL and NOEL levels are not uniformly available for all species or sexes.
38. National Toxicology Program, Center for Evaluation of Risks to Human Reproduction, National Institute of

Environmental Health Sciences, "Draft DINP Monograph, Section 5," p.3.

39. Ibid.
40. R.M. David et al., described in Koop, Juberg, et al., "A Scientific Evaluation of Health Effects of Two Plasticizers Used in Medical Devices and Toys," p. 5.
41. Koop, Juberg, et al., "A Scientific Evaluation of Health Effects of Two Plasticizers Used in Medical Devices and Toys," p. 6.
42. Ibid., p. 10.
43. J.H. Butala, as described in Koop, Juberg, et al., "A Scientific Evaluation of Health Effects of Two Plasticizers Used in Medical Devices and Toys," p. 22.
44. Koop, Juberg, et al., "A Scientific Evaluation of Health Effects of Two Plasticizers Used in Medical Devices and Toys," p. 24.
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48. Ibid., p. 440.
49. Koop, Juberg, et al., "A Scientific Evaluation of Health Effects of Two Plasticizers Used in Medical Devices and Toys," p. 25.
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52. Ibid.
53. Ibid.
54. Koop, Juberg, et al., "A Scientific Evaluation of Health Effects of Two Plasticizers Used in Medical Devices and Toys," p. 24.
55. Green, *Seeking Safety in a Dangerous World*.
56. Koop, Juberg, et al., "A Scientific Evaluation of Health Effects of Two Plasticizers Used in Medical Devices and Toys," p. 16.
57. Ibid., p. 17.
58. Ibid., p. 17.
59. Fastats, A to Z, (www.cdc.gov/nchswww/fastats/insurg.htm and www.cdc.gov/nchswww/fastats/ outsurg.htm).
60. See "blood facts" at America's Blood Centers web site (http://www.americasblood.org/).
61. Correspondence with Rod Taber, Salter Laboratories. Number of Americans maintaining long-term chronic oxygen therapy from American Lung Association