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SAFETY OF PHTHALATES AND BISPHENOL-A IN EVERYDAY CONSUMER PRODUCTS

HEARING

BEFORE THE

SUBCOMMITTEE ON COMMERCE, TRADE, AND CONSUMER PROTECTION

OF THE

COMMITTEE ON ENERGY AND COMMERCE

HOUSE OF REPRESENTATIVES

ONE HUNDRED TENTH CONGRESS

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[1] Mr. Rush did not submit a prepared statement.
[2] Dr. Babich did not answer submitted questions for the record.
[3] Dr. Bucher did not answer submitted questions for the record.
[4] Dr. Alderson did not answer submitted questions for the record.
[5] Ms. Stanley did not answer submitted questions for the record.

SAFETY OF PHTHALATES AND BISPHENOL-A IN EVERYDAY CONSUMER PRODUCTS

TUESDAY, JUNE 10, 2008

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON COMMERCE, TRADE,
AND CONSUMER PROTECTION,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, DC.

The subcommittee met, pursuant to call, at 10:08 a.m., in room 2322 of the Rayburn House Office Building, Hon. Jan Schakowsky (vice chair of the subcommittee) presiding.

Members present: Representatives Schakowsky, Barrow, DeGette, Hooley, Melancon, Whitfield, Stearns, Pitts, Terry, Sullivan, Burgess, and Blackburn.

Staff present: Judy Bailey, Valerie Baron, Andrew Woelfing, Consuela Washington, Christian Fjeld, Megan Mann, Lauren Bloomberg, Jodi Seth, Chad Girand, Will Carty, and Shannon Weinberg.

Ms. SCHAKOWSKY. The meeting of the Subcommittee on Commerce, Trade, and Consumer Protection will come to order. I will begin with my opening statement, but before I do that I would like to recognize the absence of our subcommittee chairman, my friend and colleague, Representative Bobby Rush. As you all know, Chairman Rush is recuperating in Chicago right now. Although he is not here today, he is in regular touch with his staff. He is fully involved in the legislative matters before this subcommittee, and I know that he is being ably represented by his staff in his absence. On behalf of all the members of this subcommittee, I want to wish him a speedy recovery, and we are all looking forward to having him back here in this chair.

At this time, I would like to ask unanimous consent to insert Chairman Rush's testimony in the record. Without objection, so ordered.[The prepared statement of Chairman Rush was unavailable at the time of printing.]

OPENING STATEMENT OF HON. JAN SCHAKOWSKY, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF ILLINOIS

Ms. SCHAKOWSKY. I will now recognize myself for 5 minutes for the purpose of an opening statement. We are here today to discuss the safety of using phthalates and bisphenol-A in consumer products. Currently, phthalates are used in a wide variety of products such as toys, cosmetics, furnishings, footwear, and luggage to make plastics softer and more flexible. BPA is used to make plastics harder and shatter resistant and can be found in protective gear

such as helmets, goggles, electronics, pacifiers, shields, and CDs, as well as a wide variety of applications not under the jurisdiction of the subcommittee such as baby bottles, water bottles, medical devices, and dental sealants.

There is a wide and sometimes contradictory body of scientific evidence regarding the possible harm of using these substances and products. While there may be disagreement in the scientific and business community about the wisdom of a ban on these substances one thing is very clear: there is widespread and serious concern about the safety of these products. Almost a decade ago, the 23 member countries of the European Union banned six phthalates in all children's products. In response, Toys"R"Us, Mattel, and Hasbro all soon followed suit and announced that they would stop manufacturing children's toys made with phthalates worldwide. Fourteen other countries have joined the EU in banning these phthalates as well.

In America, two particular phthalates, DEHP and DINP, were voluntarily removed from infant products such as teethers and soft rattles in 1999 after the Consumer Product Safety Commission issued an inconclusive study that called for more research into their potential hazard. Last year, California became the first state in the nation to ban six phthalates from children's products. In April, Washington State became the second state to do so. In Congress, Representative Darlene Hooley, who is with us on the subcommittee, has introduced legislation to ban phthalates in certain products, and Senator Diane Feinstein has introduced similar legislation, including an amendment to H.R. 4040, the Consumer Product Safety Modernization Act, which the House passed in December, and which is currently in conference.

With regard to BPA, in April, 2008, the National Institute of Health National Toxicology Program issued a draft report on BPA and classified it as a chemical of "some concern" to infants and small children. Less than a week later, both Toys"R"Us and Wal-Mart announced that they would no longer sell baby bottles that were made with it. Legislation has been introduced in the Illinois state legislature that would ban both BPA and phthalates from children's products, and in Congress the Oversight and Investigations Subcommittee of the Committee on Energy and Commerce has begun an investigation into the use and possible harms of using BPA.

A wide range of over 50 children's health, women's health, environmental health, and consumer groups have come out in support of a ban of most phthalates from children's products citing ample scientific evidence that phthalates may be found in high levels in individuals across the country, and that they cause a wide variety of adverse health effects in humans. Specifically, these studies show that phthalates act as endocrine disrupters which cause potential harm to testosterone development and the male reproductive tract, early onset puberty in girls and thyroid dysfunction. Likewise, many advocates believe that BPS may cause detrimental effects on sexual development in both men and women and reproductive abnormalities. They are particularly concerned that all of these substances may affect infants in their development later in life.

The chemical industry has argued conversely that the use of phthalates and BPA in commercial levels is safe. They argue that banning phthalates may cause a significant market disruption that would leave children and consumers without access to a variety of toys and products. They have also raised concerns that banning the substances may force manufacturers to use other substances whose safety is yet unknown. This hearing will give members of the subcommittee the opportunity to explore the research into the possible harmful consequences of exposure to BPA and phthalates to consumer products and to begin to consider what policies thus address those potential harms.

I think we all agree that we need to address the legitimate concerns that are raised when we discuss banning phthalates and BPA. Will replacing phthalates with other chemicals lead to other unanticipated health risks? Are there alternative chemicals available that we can be confident are safe? Is industry prepared, able, and willing to quickly adapt their processes? On the other hand, I hope that we can all agree that if these chemicals pose a real health risk to children, we must act quickly to remove them from our shelves. I have here two rubber duckies. I can't tell the difference between them. They look and feel almost exactly the same. They cost about the same amount of money. One is manufactured with phthalates. It is almost 2 percent DNOP and DINP, and one without.

It is easy to see how a child would put either of these in their mouths. If we know one is safe, why wouldn't we remove the possibility of danger from our children's hands and mouths? As a grandmother, I am concerned that these substances left on the market may cause significant harm to our children. I am concerned that by not acting quickly, we will make the same mistakes we made in the past with lettuce, asbestos, pesticides, tobacco, and expose our children to substances which will permanently damage their development. I look forward to addressing these issues and other questions with our distinguished body of panels here today. I would like to welcome all of our witnesses and look forward to hearing each of your testimonies. And now I will recognize Mr. Whitfield, our ranking member, for 5 minutes to make an opening statement.

OPENING STATEMENT OF HON. ED WHITFIELD, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF KENTUCKY

Mr. WHITFIELD. Chairman Schakowsky, thank you very much for holding this important hearing. I might note it is the first hearing that we have held on this particular subject looking at these two ingredients. I also want to extend our best wishes to Chairman Rush. As you indicated in your opening statement, we know that he has had some significant health problems, but we hear good things about his recuperating and wish him a speedy recovery.

Obviously, all of us are very much concerned, and it is a priority for all of us when we talk about the safety of children and the people of this country. And I think it is important, as I said, that we have this hearing to look at these particular chemicals: BPA and these phthalates.

I might add that the European Union was the first governmental body to restrict or ban phthalate use, and then they concluded a study after effectuation of that ban which demonstrated several of the banned or restricted phthalates really pose no risk to human health at all. And on BPA there has been no scientific evidence that I am aware of that has demonstrated that that might be a danger to anyone. And I think because we have the Consumer Product Safety Commission reform bill that has passed the House and Senate and will soon be going to conference, an effort has been made to include in that reform bill a ban of some phthalates. And so this hearing certainly is timely because it is important. We are going to take that bill up, and we are going to have to make some decision about it.

But I think it is important. I am delighted we have our scientists here today, our witnesses here today, who certainly have much more knowledge about this than any of us do and will provide us information that will help us make hopefully the right decision. I would say that one of the companies that will benefit with the ban of BPA, for example, actually went around and was making statements and comments and speeches with groups like the People for Children's Health and Environmental Justice, saying that this product has arsenic in it, and our product does not have arsenic in it, and he was referring to BPA, and it is my understanding that BPA does not have arsenic in it. But when we try to make decisions like this certainly the priority is the health and safety of everyone, but we also have to look at what is going to be additional cost involved.

We also have to look at does the substitute product work as well as the old product, so I don't think any of this is just totally clean-cut, and it is important that we have this hearing, so I want to thank the chairman for having the hearing. We look forward to the testimony today because as I said we are going into the conference on the Consumer Product Safety Commission reform bill, and this is one of the issues that is going to be considered there. So with that, I will yield back the balance of my time.

Ms. SCHAKOWSKY. Thank you, Mr. Whitfield. I recognize the congresswoman who has probably the most expertise with this in terms of introducing legislation, and that is Congresswoman Darlene Hooley.

OPENING STATEMENT OF HON. DARLENE HOOLEY, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF OREGON

Ms. HOOLEY. Thank you, Madam Chair. I first of all would like to thank Chairman Rush for keeping his promise to hold this important hearing and thank Congresswoman Schakowsky for chairing the hearing today, and of course I thank all of you for being here and testifying. Phthalates are chemicals found everywhere in modern life and are the most commonly used plasticizers to make plastics flexible. Phthalates are used in all sorts of products but most importantly for today's hearing, children's products. When children chew on these products, phthalates leach out of them. Phthalates are one of the most heavily studied plasticizers, and some of the most recent and published studies point to what

has been called phthalate syndrome, which causes adverse reproductive effects seen in male offspring.

Although I agree with some testifying today that we are not yet at a place where we can say definitively what the direct result of phthalates exposure are, there are certainly a growing body of evidence pointing to a causal link between phthalate exposure and serious harm to pregnant women and children. The question this committee needs to ask itself is this: at what point does a body of evidence, albeit inconclusive, pointing to serious harm to our most vulnerable and precious citizens outweigh the possible minor inconvenience to the toy manufacturers that have decided not to use a safe alternative? Should we wait for irrefutable proof before we act? I believe the answer is no. Although I do not believe that the existing evidence supports a universal ban on phthalates in all products, I do believe it supports banning them from children's products.

That is why earlier this year I introduced the Children's Chemical Risk Reduction Act in cooperation with Senator Feinstein. H.R. 4030 is similar to the actions taken by California and the UE that have already banned the six most commonly used phthalates. I urge the conferees of the H.R. 4040 to join the EU, 14 countries, California, Washington, and include conference language that would ban phthalates for children's products. Although I have been involved in consumer issues my entire life joining this subcommittee has given me the opportunity to look at issues like this. The issue of phthalates highlights a striking contrast between European and U.S. regulatory approaches when it comes to actions on potentially toxic chemicals. I think Robert Donkers, the EU's environmental counselor, said it well. Unlike the United States, we don't wait until we have 100 percent proof. If there is fear, scientific suspicions that a chemical could cause irreversible damage in the future, we don't wait. By the time it is definitively proven, it could be much too late to do anything about it.

Ironically, the EU's decision to ban phthalates in children's toys was based to a large degree on evidence generated by American scientists, much of the funding by the U.S. government, including Dr. Earl Gray and Dr. Shanna Swann. I hope we address the following issues today. What does the science say regarding phthalates? How are other countries dealing with this issue? Are there safe alternatives to phthalates available? Will a phthalate ban cause U.S. market disruption? I would also like to enter into the record several letters in support of my legislation. I look forward to hearing from both panels today and working with my colleagues on addressing this very serious problem. Thank you.

Ms. SCHAKOWSKY. Now, Mr. Stearns, for your 5-minute opening statement.

OPENING STATEMENT OF HON. CLIFF STEARNS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF FLORIDA

Mr. STEARNS. Good morning, and thank you, Madam Chairwoman. I also want to reiterate Mr. Whitfield's and your comments for our concerns and prayers for the chairman, Bobby Rush, and hope that he will be back with us soon. We miss him and appre-

ciate the opportunity to have this hearing, and at his urging we are doing it.

When you look at this issue, you realize that for almost 50 years phthalates have been used in almost every different type of product, whether it is toys or furnishings or medical tubing, pacifiers and rattles. It was actually voluntarily stopped in the 1980s by the U.S. industry itself. Then when you look at BPA, it is present in food containers, plastics, also in liners, can liners, bike helmets, adhesive to baby diapers. So, you have this present sense of these two chemicals, and without bringing alarm to the public, we need to understand from our experts what is the danger and be sure we have good science behind our recommendations as well as good regulations so we don't have 50 states that have 50 different regulations to make it almost impossible for manufacturers to supply these important products.

I think we are having this hearing, and perhaps it is timely in the sense that as others have pointed out that the Consumer Product Safety Commission bill, which will be on the floor shortly, is now in conference between the Senate and the House. I am one of the ones that serve as a conferee, and I look forward to making sure that phthalates and the BPA conditions that are brought out perhaps by our witnesses today will be part of this bill. So the witnesses that we have today have a timely opportunity to recommend things that we could perhaps put in legislation. This bill will pass overwhelmingly under suspension so your time is going to be very well spent in proposing what solutions we should provide.

So, Madam Chairman, we need certainly to perhaps even have a second hearing on this. Actually, as we move into regulation and examine the science of what the implementation would mean. So I look forward to this hearing, and I again commend Mr. Rush for pushing forward with this important subject. I yield back.

Ms. SCHAKOWSKY. And now the gentleman from Georgia, Mr. Barrow.

Mr. BARROW. I thank the chair. I cannot improve upon the opening statement of either the chair or Ms. Hooley, so I will yield the opportunity to make an opening. I will waive and reserve my time for questions.

Ms. SCHAKOWSKY. Thank you. The gentleman from Texas, Dr. Burgess. Then we will have the gentlewoman from Tennessee, Ms. Blackburn.

OPENING STATEMENT OF HON. MARSHA BLACKBURN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TENNESSEE

Ms. BLACKBURN. Thank you, Madam Chairman, and I do want to welcome all of our witnesses today. I appreciate your willingness to take up the technical debate regarding the health and safety value of phthalates and BPA. These are, as you have heard, two common chemicals in consumer products, and the courage wading into this issue is not in question nor is the intrinsic value of the subject matter itself given the health and safety concerns raised by numerous products that the chemicals contribute to. What is in question on my part is the timing of the hearing. Given a lack of scientific consensus regarding the research prompting criticism re-

sponsible for the hearing, it appears more appropriate to address what every member on this dais already knows, that the No. 1 consumer issue today in this country is the price of gasoline at the pump.

And, Madam Chairman, I think there is no debate that consumers in my Tennessee district are paying a lot more to fill up their tanks than at any other time in American history. On January 7, 2007, in Shelby County, Tennessee we were at $1.96, today that is $3.86 a gallon, so it has gone from $1.96 a gallon to $3.86 a gallon. That is nearly a $2.00 difference since the majority took control of Congress of the gavels, and what we are seeing is this record increase. And this is something that many people are calling a crisis, and that we agree is a crisis and needs to be addressed today. So the No. 1 consumer issue in my district is the price at the pump.

I am disappointed that this committee is not taking time to look at that issue and to take some action on that issue. Now, Madam Chairman, I also am looking forward to a discussion about this issue at the appropriate time and to the merits of research prompting the criticism of phthalates and BPA in consumer products. I have a grandchild who was just born. My very first grandchild is now 1-month old, and I am looking more closely than ever at all of these products. And I am also looking at the price of fuel as we come and go with that grandchild. So I will have to say that I have had no constituents ask me what are we doing on the presence of BPA and phthalates and the chemicals in plastics, but what I have every single day over and over is a question from consumers when in the world is Congress going to take some action on the price of gas at the pump. I yield back the balance of my time.

Ms. SCHAKOWSKY. And now the gentleman from Louisiana, Mr. Melancon. OK. Let us try and keep track of everyone here. And now the gentleman from Texas, yes, he is here, Dr. Burgess.

OPENING STATEMENT OF HON. MICHAEL C. BURGESS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Mr. BURGESS. Thank you, Madam Chair. It is an interesting hearing we have before us today, and I am looking forward to learning a good deal more about a subject of which I probably don't know enough, but I am concerned about what the science has to say. I think that has got to be first and foremost in our minds. It seems as if perhaps industry and the public has gotten ahead, certainly ahead of this committee, which is no surprise, with the head of the science and the restructuring of the consumer products that are out there. And the other question is, is drastic action needed, and the answer right now from what I can tell is the science is inconclusive and drastic action, well, perhaps not yet, but as has already been pointed out some action is being taken.

I do share some concerns that have previously been voiced by our chairman, Mr. Rush, who is not with us today, that if we do not complete the scientific information and in fact there is a problem and it is unknown whether one of the unintended consequences will be that perhaps the products that we would like to see removed will only end up in the discount houses and the resale shops in some of the poorer neighborhoods represented by Mr. Rush and

indeed the poorer neighborhoods represented by myself. So I do want us to do a thorough and careful job on this. I don't think we can abrogate that responsibility. It is my understanding that some of the testing done in regards to these chemicals involves using a syringe to inject the chemicals into the brain of laboratory rats. I will submit that people do things in unusual ways. I never cease to be amazed at the inventiveness of people, but I don't recall hearing about anyone injecting themselves with phthalates or BPA into their brain.

So some of the studies perhaps seem to be situations that you would never find in common clinical practice. I do want to say one thing about the timing of this hearing. It has already been mentioned that H.R. 4040, Consumer Product Safety Commission reauthorization is in conference right now. It is my understanding that the principals have yet to meet in conference. The legislation surrounding these products was introduced on the Senate side and never on the House side, and I hope we are not using this hearing today as an excuse to put something hastily into that conference report and then have that come to the floor without the House having done its due diligence and its work on understanding the science of these compounds, so we have got a lot to get through today. Madam Chairwoman, I yield back the balance of my time.

Ms. SCHAKOWSKY. Seeing no other members, I want to at this time welcome our witnesses and introduce the first panel. We have Dr. Michael A. Babich, a chemist at the Directorate for Health Sciences of the Consumer Product Safety Commission. Dr. Babich focuses on risk assessments of chemicals found in consumer products. We have Dr. John Bucher, Associate Director of the National Toxicology Program at the National Institute of Environmental Health Sciences, part of the National Institutes of Health. Dr. Bucher is a pharmacologist and is responsible for oversight of the National Toxicology Program's review of BPA. Dr. Bucher is also responsible for toxicology and carcinogenesis studies, the NTP report on carcinogens, and the NTP center for the evaluation of risks to human reproduction. Dr. Norris Alderson is Associate Commissioner for Science at the Food and Drug Administration. Dr. Alderson is responsible for coordination of science issues across the agency, the Office of Women's Health, Office of Orphan Product Development, the Good Clinical Practices Staff, oversight of FDA sponsored clinical studies, research integrity, standards coordination, and scientists peer review. Dr. L. Earl Gray, Jr. is a research biologist with the Environmental Protection Agency. Dr. Gray's work on phthalates has focused on effects of phthalate mixtures. He serves on the editorial board of the Journal of Toxicology and Environmental Health.

I will ask the witnesses if they have opening statements to please take up to but no more than 5 minutes for your opening statement. We will begin from my left, your right, with our first witness, Dr. Babich.

STATEMENT OF MICHAEL A. BABICH, PH.D., CHEMIST, CONSUMER PRODUCT SAFETY COMMISSION, BETHESDA, MARYLAND

Dr. BABICH. Good morning, Madam Chair and committee members. I am Dr. Michael Babich, a chemist in the Directorate for Health Sciences at the U.S. Consumer Product Safety Commission. It is my pleasure to come before you today to offer testimony on phthalates and bisphenol-A. CPSC's regulatory authority over chemical substances stems from the Federal Hazardous Substances Act or FHSA. Under the FHSA, CPSC must consider both toxicity and exposure to determine whether a product may be considered a hazardous substance. Children's products containing a hazardous substance are automatically banned.

Phthalates are chemicals that are added to the plastic polyvinyl chloride or PVC to make it flexible. There are several types of phthalates present in a variety of consumer products. In the early 1980s the primary phthalate used in children's products was di-2-ethylhexyl phthalate, DEHP. When a National Toxicology Program study showed that DEHP caused cancer in animals, CPSC initiated a regulatory proceeding. The regulatory proceeding was withdrawn, however, when manufacturers voluntarily removed DEHP from teethers, rattles, and pacifiers. A voluntary ban was later incorporated into the ASTM toy standard, and DEHP was replaced with another phthalate, diisononyl phthalate or DINP.

In November, 1998, the Commission received a petition requesting a ban of PVC in children's products due in part to concern about phthalates. In December of 1998, manufacturers voluntarily agreed to stop using DINP in teethers, rattles, and pacifiers. When manufacturers voluntarily removed DINP from these products they had two options: replace PVC with another plastic that does not require a plasticizer or substitute another type of plasticizer for DINP. None of the substitutes is as well studied as DINP and for some substitutes little or no toxicity data are available. To assess the potential health risks from DINP, CPSC staff collaborated with scientists in Europe and Canada to develop a laboratory method to measure the migration of DINP from products.

The staff conducted an observational study of children's mouthing behavior, and the Commission convened a Chronic Hazard Advisory Panel or CHAP to review the potential health risks associated with DINP. The CHAP concluded that for DINP to pose a risk of injury to young children, they must routinely mouth DINP containing toys for at least 75 minutes per day. For the majority of children, the CHAP concluded that exposure to DINP would pose a minimal to non-existent risk of injury. The staff's observational study, completed after the CHAP's report, showed that mouthing times for these products were much lower than the 75 minutes per day that the CHAP identified as a minimum level of concern.

The staff estimated that the upper-bound DINP exposures from mouthing these products were 100 times below the acceptable daily intake. Therefore, CPSC staff concluded that exposure to DINP in these products did not present a health risk to children. In February of 2003, the Commission voted unanimously to deny the petition requesting a ban of PVC in children's products.

Bisphenol-A or BPA is a chemical used to make polycarbonate plastics and epoxy resins. Most human exposure to BPA comes from food. According to the recent report from the National Toxicology Program, Center for the Evaluation of Risk to Human Reproduction, as much as 99 percent of BPA exposure to children is from food. The products that have the greatest potential for BPA exposure are under the jurisdiction of the U.S. Food and Drug Administration.

Polycarbonate is also used in some products that fall under CPSC's jurisdiction, including compact disks, protective eyewear, shatter resistant windows, helmets, and other protective equipment. It is used in these products because of its strength, and the BPA exposure from these products is likely to be negligible. In considering proposals to ban phthalates and BPA in children's products, it is important to consider that there is little information about the toxicity of some DINP substitutes. Additionally, the important role of polycarbonate in protective equipment and safety glass should be considered. A ban of BPA in children's products could result in less effective protection from head, eye, and other injuries.

Thank you for the opportunity to speak to you today. I will be happy to answer your questions.

[The prepared statement of Dr. Babich follows:]

U.S. Consumer Product Safety Commission

TESTIMONY OF DR. MICHAEL BABICH, U.S. CONSUMER PRODUCT SAFETY COMMISSION

SUBMITTED TO THE SUBCOMMITTEE ON CONSUMER AFFAIRS, INSURANCE AND AUTOMOTIVE SAFETY

June 10, 2008

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Testimony of Dr. Michael Babich
Directorate of Health Sciences,
U.S. Consumer Product Safety Commission
June 10, 2008

Good Morning, Mr. Chairman and Members of the Committee:

My name is Dr. Michael Babich, and I am a chemist in the Directorate of Health Sciences at the U.S. Consumer Product Safety Commission (CPSC). I am pleased to come before the Committee today to testify and to answer your questions regarding phthalates and bisphenol A.

Phthalates are chemicals used to soften polyvinyl chloride (PVC) and make it flexible. PVC is found in a number of consumer products. CPSC's regulatory authority over phthalates comes from the Federal Hazardous Substances Act (FHSA), and since the early 1980's, the CPSC has investigated, researched, and monitored phthalates used in consumer products under the agency's jurisdiction.

In regulating a product under the FHSA, the CPSC must consider not only the toxicity of the product under consideration but also the exposure to that product under reasonably foreseeable handling and use. If such a product may cause substantial personal injury or substantial illness during or as a proximate result of any customary or reasonably foreseeable use by children and is a toy or other article for use by children, it would be considered a hazardous substance and is automatically banned by operation of law. The FHSA does not provide for pre-market approval of consumer products.

In the early 1980's the primary phthalate used in children's products was di-(2-ethylhexyl) phthalate or DEHP. A National Toxicology Program 2-year bioassay indicated that DEHP caused cancer in rodents. Because of concern about these results, the industry removed DEHP from pacifiers, rattles, and teethers. A ban of the use of DEHP in pacifiers, rattles and teethers was subsequently incorporated into ASTM F-963, the voluntary Standard Consumer Safety Specification on Toy Safety. DEHP was replaced with another phthalate, diisononyl phthalate or DINP.

Chronic toxicity studies on DINP were completed by the chemical industry in 1997 and 1998. In 1998 CPSC staff completed a risk assessment on DINP. While staff concluded that few, if any, children were at risk of liver or other organ toxicity from mouthing teethers, rattles, and other PVC toys that contain DINP, staff also indicated that there were a number of uncertainties, primarily regarding exposure. As a result of these uncertainties, a voluntary agreement was reached with industry in December 1998 to stop the use of DINP in teethers, rattles, and pacifiers.

Additionally, CPSC staff at that time recommended that the Commissioners convene a Chronic Hazard Advisory Panel (CHAP) to evaluate whether there are chronic hazards

associated with exposure to DINP and what, if any, risk is posed.[1] The staff further recommended: 1.) that the Commission conduct an extensive observation study of children's mouthing behavior to better understand the exposure issues; 2.) develop a better laboratory method to measure the migration of DINP, and 3.) test additional products intended for children under three years of age to determine if they contain phthalates. The Commission approved all of these staff recommendations.

In its report to the Commission on June 15, 2001, the CHAP concluded that for DINP to pose a risk of injury to young children, they must routinely mouth DINP-plasticized toys for 75 minutes per day or more. For the majority of children, they concluded that exposure to DINP from DINP-containing toys would be expected to pose a minimal to non-existent risk of injury and, at the levels to which children were exposed, there was no carcinogenic, reproductive or developmental risks.

CPSC's behavioral observation study took place in 2000 and 2001. It was not completed in time for the CHAP to utilize the results when reaching their conclusions. In the behavioral observation study, trained observers monitored the behavior of 169 children between the ages of 3 and 36 months. The study found that the daily mouthing times of toys and teethers were much lower than expected. Based upon this observation study, staff concluded that it is very unlikely that children will mouth soft plastic toys for the 75 minutes a day that the CHAP identified as a minimum level of concern.

In a separate study, CPSC staff measured the level of migration of DINP from 41 children's products purchased from retail stores. The scientific experiments conducted in this study measured the amount of DINP that would leach from a representative sample of toys when children placed them in their mouths. Taking all of this information together, the CPSC staff estimated that the daily DINP exposure from toys on the market at that time for children up to 3 years of age would not pose a health risk.

In November 1998, a group of organizations petitioned the Commission to ban children's products made from PVC. Based upon the extensive scientific and technical investigations described above, staff concluded in its briefing package to the Commissioners that there is no demonstrated health risk posed by PVC toys or other products intended for children 5 years of age and under, and thus, no justification for banning PVC use in toys and other products for children 5 years of age and under. On February 21, 2003, the Commission voted 3-0 to deny the request to ban PVC in all toys and other products intended for children five years of age and under. A copy of the petition denial letter, Record of Commission Action, and Commissioners' statements are attached.

I would like to note that the legislation currently under consideration by Congress would ban certain phthalates down to 0.1%. Because phthalates are ubiquitous, the level of 0.1% would be a background level and not the result of phthalate being intentionally added to the product. When we tested toys, we found that phthalates were present in the range of 13 to 39%; that is

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[1] A CHAP is an independent panel of seven scientists chosen by the Commission from scientists recommended by the National Academy of Sciences. A CHAP is required under the Consumer Safety Act before the Commission may regulate a chronic hazard.

what is needed to make toys flexible. For toys containing multiple phthalates, it could be extremely difficult to measure down to the level of less than 0.1%.

Also, should DINP be banned in all children's products, manufacturers could choose to use another plasticizer that may or may not be as well characterized toxicologically as DINP. They might choose to use another plastic other than PVC which may release a more toxic chemical and which may or may not be toxicologically characterized. The new plastic may not have the characteristic of flexibility which PVC has and which minimizes the production of small parts that could pose choking hazards.

With regard to bisphenol A, or BPA, this is a chemical used in the manufacture of polycarbonate plastics and epoxy resins. Small amounts of BPA may be released as the plastic or resin breaks down. Examples of consumer products using polycarbonate plastics include eyeglass lenses, protective eyewear, protective gear such as helmets and shin guards, glazing, electronics, compact disks and labware. Epoxy resins are used in paints, coatings, adhesives, and as linings for canned foods.

Polycarbonate used in pacifier shields, helmets, protective gear such as goggles and shin guards, as well as other products, would fall under CPSC's jurisdiction. However, since polycarbonates are expensive, it is our understanding that polycarbonate is used in only those consumer products where there is a need for a very hard, unbreakable, sturdy plastic. Polycarbonate is used in pacifier shields (that prevent the nipple from being swallowed) so that when a child falls, the shield does not shatter, breaking into small parts and injuring the child. There would be no exposure expected from helmets, goggles, other protective gear, compact disks, or electronics. If there is no exposure, there is no health risk. Polycarbonate plays a very important role in its use in helmets and other protective gear. The helmets prevent children from receiving serious head injuries while engaging in many sports. This beneficial use of polycarbonate should be considered when acting to ban bisphenol A from children's products. Such a ban could result in less effective protection of children from head, eye, or bodily injury.

The greatest potential for human exposure to BPA is from food contact items. The recent in-depth peer review conducted by the National Toxicology Program (NTP) Center for the Evaluation of Risk to Human Reproduction (CERHR) stated that diet accounts for the vast majority, 99%, of human exposure. If BPA migrates out of a food contact surface into food, it is considered an unintentional food additive and would be under the jurisdiction of the Food and Drug Administration (FDA).

Thank you for the opportunity to testify today, and I welcome your questions.

U.S. CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, DC 20207

Record of Commission Action
Commissioners Voting by Ballot*

Commissioners Voting: Chairman Hal Stratton
Commissioner Thomas H. Moore
Commissioner Mary Sheila Gall

ITEM:

Petition (HP 99-1) Requesting Ban of Use of PVC in Products Intended for Children Five Years of Age and Under

DECISION:

The Commission voted unanimously (3-0) to deny petition HP 99-1 and issue a denial letter as drafted (copy attached). The petition requests a ban of polyvinyl chloride (PVC) in all toys and other products intended for children five years of age and under and requests that the Commission issue a national advisory warning of health risks associated with soft plastic vinyl toys.

Commissioners Gall and Moore each submitted statements to accompany their votes. The petition denial letter and the Commissioners' statements are attached.

For the Commission:

Todd A. Stevenson
Secretary

* Ballot vote due February 20, 2003

U.S. CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, DC 20207

Tel: 301 504-7923
Fax: 301 504-0127
Email: tstevenson@cpsc.gov

February 26, 2003

Mr. Jeffrey Becker Wise
Policy Director
National Environmental Trust
1200 18th Street, NW, Suite 500
Washington, DC 20036

Re: Petition Requesting Ban of Use of Polyvinyl Chloride (PVC) in Products Intended for Children Five Years of Age and Under **(briefing package date corrected as noted in bold)**

Dear Mr. Wise:

As requested in your letter of November 19, 1998 I am communicating through you to advise the petitioners that on February 21, 2003, the Consumer Product Safety Commission voted 3-0 to deny the requests from the National Environmental Trust and eleven other organizations that the Commission:

- immediately ban polyvinyl chloride (PVC) in all toys and other products intended for children five years of age and under; and

- issue a national advisory on the health risks that have been associated with soft plastic vinyl toys to inform parents and consumers about the risks associated with PVC toys currently in stores and homes.

The submission from the petitioners gave as the primary reason for these requests the toxicity of diisononyl phthalate (DINP), a plasticizer in PVC, and the toxicity of lead and cadmium in PVC.

The requested ban on PVC in all toys and other products intended for children five years of age and under was docketed as a petition for rulemaking under section 3(j) of the Federal Hazardous Substances Act (FHSA) on December 7, 1998 (Petition No. HP 99-01). 15 U.S.C. §1262(j). The request that the Commission issue a national advisory on the health risks that have been associated with soft plastic vinyl toys was not docketed because it would not require rulemaking to implement.

To take the requested regulatory action, the Commission would have to declare under the FHSA that products containing PVC intended for use by children of five years old and younger were "hazardous substances." This would require the Commission to find that such PVC products met the FHSA's definition of hazardous substance, which requires in this instance not only that the product be toxic, but that it "may cause substantial personal injury or substantial illness during or as a proximate result of any customary or reasonably foreseeable handling or use, including reasonably foreseeable ingestion by children." 15 U.S.C. § 1261(f)(1)(A).

In making a decision whether to grant a petition and commence rulemaking, the Commission is to consider, *inter alia*, the following factors:

- Whether the product involved presents an unreasonable risk of injury
- Whether a rule is reasonably necessary to eliminate or reduce the risk of injury
- Whether failure of the Commission to initiate the rulemaking proceeding requested would unreasonably expose the petitioner or other consumers to the risk of injury which the petitioner alleges is presented by the product

16 CFR § 1051.9

The ban rulemaking would be conducted under section 3(a) of the FHSA.[1] Section 3(a)(2) of the FHSA requires that a rulemaking such as the one requested be conducted in accordance with section 701(e) of the Federal Food, Drug, and Cosmetic Act (FDCA).[2] Under section 701(e), for the Commission to proceed to rulemaking, the petition must set forth "reasonable grounds" for the requested action. The United States Court of Appeals for the District of Columbia Circuit has held that "reasonable grounds" for a petition under the FHSA "are grounds from which it is reasonable to conclude that the Commission would be able to make the findings required to issue the requested rule and to support those findings with substantial evidence on the record."[3]

The Commission considered the petition and the materials submitted with it; the June 15, 2001 final report of the Chronic Hazard Advisory Panel (CHAP) on DINP convened in accordance with sections 28 and 31 of the Consumer Product Safety Act, 15 U.S.C. §§ 2077, 2080; a CPSC staff behavioral observation study to determine how much time young children actually spend mouthing objects and the types of objects they mouth; the November 1997 Commission staff report entitled, *CPSC Staff Report on Lead and Cadmium in Children's Polyvinyl Chloride (PVC) Products*; the 488 public comments received on the petition; the staff briefing package dated **August 13, 2002**; information presented by the staff during an oral

[1] 15 U.S.C. § 1262(a).
[2] 21 U.S.C. § 371(e).
[3] *Consumer Federation of America v. CPSC*, 883 F.2d 1073, 1076 (D.C. Cir. 1989).

briefing on November 8, 2002; comments received on the staff briefing package; and other information.

The staff briefing package recounts the extensive scientific and technical investigations that have been carried out by the CPSC and others on the issue of PVC in products intended for children and concludes as follows.

> Based upon the scientific data presented in this briefing package, the staff believes that there is no demonstrated health risk posed by PVC toys or other products intended for children 5 years of age and under and thus, no justification for either banning PVC use in toys and other products intended for children five years of age and under or for issuing a national advisory on the health risks associated with soft plastic toys.

Memorandum from Marilyn L. Wind, Ph.D., Deputy Associate Executive Director, Directorate for Health Sciences, to the Commission, *Response to Petition HP 99-1*, **August 13, 2002,** at 16-17.

That conclusion is based in part on the finding of the DINP CHAP that, "[f]or the majority of children, the exposure to DINP from DINP-containing toys would be expected to pose a minimal to non-existent risk of injury." *Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Diisononyl Phthalate (DINP)*, June 2001, Executive Summary item 17. The new data from the recent CPSC behavioral observation study reported in the staff briefing package, which was not available at the time of the CHAP's deliberations, confirm this conclusion and demonstrate that children are exposed to DINP at even lower levels than the CHAP assumed when they reached their conclusion. Further, the recent survey of toys mouthed by children under the age of three also reported in the staff briefing package shows that not all soft plastic toys contain DINP. Therefore, exposure would be even less than the CHAP predicted because children mouth these toys for less time per day than the CHAP estimated, and the average amount of DINP in toys mouthed by children under the age of three is less than the CHAP estimated. If the risk to children under the age of three is not sufficient to warrant action, then based upon the data collected in the staff's behavioral observation study, and the data available in published literature, which indicate that mouthing declines as children age, there is no basis for the findings necessary under the CPSC regulations governing grant or denial of petitions or the FHSA for the Commission to take the requested actions with respect to DINP in PVC toys and other products intended for children five years of age and under.

With respect to lead and cadmium, in November 1997, the Commission staff issued a report entitled, *CPSC Staff Report on Lead and Cadmium in Children's Polyvinyl Chloride (PVC) Products*. That report detailed the results of testing the Commission staff conducted on children's products that Greenpeace had alleged contained hazardous levels of lead and cadmium. Although some of the vinyl products identified by Greenpeace and tested by CPSC

staff contained lead or cadmium, further testing and evaluation revealed that hazardous amounts of lead or cadmium were not released from the products. This means that children would not be exposed to hazardous levels. The report concluded that children would not be exposed to hazardous levels of lead or cadmium when the products are handled or used in a reasonably foreseeable manner. Thus, there is no basis for the findings necessary under the CPSC regulations governing grant or denial of petitions or the FHSA for the Commission to take the requested actions with respect to lead or cadmium in PVC toys and other products intended for children five years of age and under.

In sum, as a result of consideration of the extensive research and analysis summarized herein, the Commission has denied the petition and declined to issue the requested national health advisory.

Sincerely yours,

Todd A. Stevenson
Secretary

Copy to:

Nancy Chuda
Director
Children's Health Environmental Coalition

Mary Ellen Fise
General Counsel
Consumer Federation of America

Rick Hind
Legislative Director
Toxics Campaign
Greenpeace USA

Justine Maloney
Washington Representative
Learning Disabilities Association

Sheila McCarron
Program Director
National Council of Catholic Women

Sammie Moshenberg
Director (Washington Office)
National council of Jewish Women

Philip Clapp
President
National Environmental Trust

Robert K. Musil, Ph.D.
Executive Director
Physicians for Social Responsibility

Jaydee Hanson
Assistant General Secretary
United Methodist Church--
General Board of Church and Society

Pamela Spar
Executive Secretary
United Methodist Church--
Women's Division

Gene Karpinski
Executive Director
U.S. Public Interest Research Group

Ed Hopkins
Vice President
Environmental Working Group

U.S. CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, DC 20207

STATEMENT OF THE HONORABLE MARY SHEILA GALL ON VOTE TO DENY PETITION REQUESTING A BAN OF POLYVINYL CHLORIDE IN TOYS AND PRODUCTS INTENDED FOR CHILDREN FIVE AND UNDER

February 20, 2003

Today I voted to deny a petition submitted by a group of organizations that asked the Commission to ban Polyvinyl Chloride (PVC) in all toys and other products intended for children aged five years and under. The Commission staff gave extensive consideration to the allegations of the petition and thoroughly examined all of the health effects alleged to be caused by children's mouthing of products made of PVC. The staff paid particular attention to products that used diisonyl phthlate (DINP) as a plasticizer. This thorough examination revealed that there is no risk posed by PVC that rises even remotely to that specified by the Federal Hazardous Substances Act (FHSA), the statute under which the Commission regulates this type of risk. Accordingly, the petition must be denied.

The Commission and its staff gave careful attention to the allegations of the petition, as they properly should when claims of detrimental health effects to children are made. A previous Commission staff risk assessment concluded that the lead and cadmium in PVC products posed no risk of injury to children and the petitioners submitted no evidence that called into question the results of that risk assessment. Assessing the risk posed by DINP in PVC involved work beyond that contained in the earlier risk assessment. The Commission went to great lengths to assess all the risks that might be posed by DINP. The staff used a method validated by two international interlaboratory studies of measuring the quantity of DINP that migrates from PVC products. The staff then used that method to estimate the amount of DINP that actually entered a child's body when a PVC product was mouthed. The Commission then convened a Chronic Hazard Advisory Panel (CHAP), which reviewed extensive toxicological data about DINP. The CHAP concluded that for the vast majority of children the exposure to DINP from PVC-containing products posed a minimal to non-existent risk of injury. Data from a subsequent Commission staff study of exposure times of children mouthing products revealed that children were exposed to even less DINP than the CHAP had assumed in making its finding. The chance that children are being injured from mouthing products made from PVC is *de minimus*. There is simply nothing in the record that remotely justifies any finding that PVC products intended for children constitute a hazardous substance within the meaning of the FHSA.

While the Commission has no legal authority to ban PVC products intended for use by children, there is toxicity data showing that it is a carcinogen in rodents, although it is a type of

cancer not usually associated with humans. As least partially in response to these toxicity findings, in 1998 the toy industry and large retail chain stores in the U.S. voluntarily agreed not to sell items made out of PVC designed to be placed in the mouth (e.g., teethers, rattles and pacifiers). The European Union and Japan reached a similar result through their own regulatory processes.

Chronic hazards are among the most technically difficult product-safety problems that the Commission considers. Unlike acute hazards, where the effects occur very quickly and are easily observable, chronic hazards involve health effects that may occur many years after exposure and which may be difficult to trace to exposure to any particular substance. Considerable scientific expertise must be brought to bear on any allegations of chronic hazards and the result must always reflect a judgment call. This may be subject to revision if more is learned about the toxicity or exposure of a specific substance. In the case of PVC, however, consumers may have a high level of assurance that soft plastic products pose no risk to children.

UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, DC 20207

STATEMENT OF THE HONORABLE THOMAS H. MOORE
ON THE PETITION TO BAN POLYVINYL CHLORIDE IN PRODUCTS INTENDED FOR CHILDREN FIVE YEARS OF AGE AND UNDER
February 21, 2003

I am voting to deny the petition to ban polyvinyl chloride in products intended for children five years of age and under. The clear weight of the evidence produced by staff supports the conclusion that children are not at risk from mouthing products currently on the market that contain diisononyl phthalate (DINP). This evidence consists of new exposure studies showing how long children mouth various objects, the migration rates of phthalates from products on the market, an Acceptable Daily Intake that has an extremely large uncertainty/adjustment factor and a scientific consensus that DINP is nongenotoxic and that the cancer caused by peroxisomal proliferation by DINP in the liver of rodents is not relevant to humans. As these are the best and most current scientific opinions, I believe the Commission must bow to that judgment. Our staff has done extraordinary work on this petition—by far the most comprehensive work done to date anywhere in the world. I congratulate them on their achievement. Both their work, and the work of the scientists who participated in the Chronic Hazard Advisory Panel on DINP, should calm parents' fears about the potential harm to young children from children's products currently on the market that contain DINP.

I am concerned, however, that the staff's conclusions could be the basis for industry to use phthalates in products that they have voluntarily agreed not to use them in, namely rattles, teethers and pacifiers. One area in which we do not have concrete information is the migration rate of DINP from these three types of children's products. Our assumption about the migration rate of phthalates from these products could prove to be too low. We also are not completely sure how much phthalates very young children are exposed to from other sources in their environment. This background exposure, coupled with the uncertainty of the rate of migration, made me consider voting to defer action on the petition until we see what happens in the marketplace as a result of the staff's conclusions. If phthalates were to be used in teethers, rattles or pacifiers in the future, the uncertainties mentioned above could cause us to be petitioned again in this area. I decided that I would not vote based on speculation of what might happen. All I can vote on today is the current state of the marketplace and of scientific knowledge, both of which lead to the conclusion that the ingestion of DINP by young children from the children's products on the market poses no risk of harm to America's children.

Ms. SCHAKOWSKY. Thank you. Dr. Bucher.

STATEMENT OF JOHN R. BUCHER, PH.D., ASSOCIATE DIRECTOR, NATIONAL TOXICOLOGY PROGRAM, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES, NATIONAL INSTITUTES OF HEALTH

Dr. BUCHER. Thank you, Madam Chairman, and good morning. I am John Bucher, Associate Director of the National Toxicology Program. The NTP is an interagency program, funded and managed by the National Institute of Environmental Health Sciences. NIEHS and NTP are part of the National Institutes of Health. The NTP carries out toxicology research and testing on substances of concern to the Federal Government and the public. We also perform literature review and analysis activities and since 1980 have produced the Report on Carcinogens. In 1998, we established the Center for the Evaluation of Risks to Human Reproduction, CERHR, which carries out literature evaluations on substances that may affect human reproduction and development.

The NTP has extensively researched phthalates for cancer and reproductive effects in animals, and through the CERHR, has reviewed the world's literature on seven phthalates for potential effects on human reproductive health. We have studied bisphenol-A, BPA, less extensively in animals, although recently we conducted a lengthy evaluation of the very large literature on the potential for BPA to affect reproduction and development. This evaluation culminates tomorrow with a public peer review of the Draft NTP Brief on Bisphenol-A before our NTP Board of Scientific Counselors. This draft brief represents our opinion of the science on BPA and is based on our evaluation to date of the literature, informed by the findings of an expert panel and with consideration of public comments solicited on five separate occasions.

BPA is a high-production industrial chemical used to manufacture polycarbonate plastics and epoxy linings of tin cans. It has been known since 1938 to mimic estrogen when given in large amounts to experimental animals. More recently, it has also been studied for its ability at very much lower doses to affect hormonal processes involved in development, when an animal is exposed as a fetus or during infancy. BPA leaches in small amounts from plastic items such as polycarbonate baby bottles and can be measured in infant formula coming from epoxy-lined cans. The 2003 NHANES survey conducted by the CDC found detectable levels of bisphenol-A in 93 percent of over 2,500 hundred urine samples from people 6 years of age and older. These data are considered representative of exposures in the United States.

The best estimates that we have suggest that the doses of BPA causing subtle effects on the development of animals are close to estimates of current exposures to the general U.S. population. Taking this information into account, the NTP reached several preliminary conclusions in our draft brief. We expressed some concern that current estimated exposures of BPA to fetuses, infants, and children could cause neural and behavioral effects, effects on the prostate and mammary gland, and an earlier age at which females attain puberty. We express negligible concern or minimal concern that current exposures to BPA could cause adverse health effects

in other segments of the population. Some concern is the midpoint of a 5-level scale. The levels are negligible concern, minimal concern, some concern, concern, and serious concern.

Although we agreed with our expert panel in expressing some concern for current exposures to BPA concerning neural and behavioral effects, we expressed an elevated level of concern, some concern, over the conclusions reached by our expert panel for changes to the prostate as well as earlier puberty in females. The expert panel did not specify a level of concern for the mammary gland. These elevated concerns were based on new literature, on clarifications provided in public comments to studies that were considered of low utility by our expert panel, and scientific justification for using data from studies utilizing non-oral routes of exposure to neonatal animals.

There are a number of uncertainties in the scientific information on BPA. The literature from experimental animal studies is large, but with many conflicting findings. There are insufficient data from studies in humans to determine directly whether BPA is affecting human reproductive health. The studies we base some concern on are not the traditional safety assessment studies done according to regulatory guidelines. Rather, they are smaller studies carried out in academic laboratories. These have often examined subtle developmental endpoints in experimental animals that are more difficult to interpret with regard to how they contribute to the weight of evidence for human health effects.

Despite the limitations of these studies, the NTP determined that because the effects in animals occur at BPA exposure levels similar to those experienced by humans, the possibility that BPA may alter human development could not be dismissed. As I mentioned earlier, the NTP Board of Scientific Counselors will review this draft brief at its meeting tomorrow, and we will take their recommendations under consideration, and the final brief will be published later this year.

Turning to phthalates, the NTP has conducted 13 cancer bioassays and 45 studies on reproductive or developmental toxicity with various phthalate esters. It has been known for more than 25 years that phthalates can affect reproduction. Fetal animals are more sensitive than newborns, which are in turn more sensitive than older animals. Not all phthalates produce adverse reproductive effects in animals, but those that do cause similar toxicity to the developing rat fetus when exposures occur during a critical window of sexual differentiation during pregnancy.

These agents induce malformations in the male reproductive tract by affecting development that is mediated through androgens, for example, testosterone, and the most severe manifestations occur with higher doses. In addition, some phthalates when administered to the developing fetus can also induce subsequent testicular tumors in the adult animal after being exposed only during the short window of pregnancy. A few small studies in humans have linked maternal exposure to specific phthalates with adverse outcomes in their children, including decreased testosterone levels in boys, but additional research is needed to confirm these findings. Failure of normal development of the testes has been proposed to explain increases in certain male reproductive problems. However, thus, far,

no cause and effect relationship has been established between any environmental agent and these specific human outcomes.

As I mentioned earlier, the CERHR has reviewed the literature on phthalates, and we expressed serious concern for male infants for whom exposure to DEHP during certain medical treatments could adversely affect development of the reproductive tract. We expressed concern for male offspring of women undergoing certain medical treatments during pregnancy or breastfeeding, and for infants less than 1 year old exposed to DEHP by diet or mouthing DEHP-containing objects. We expressed some concern for male children who may be exposed to levels of DEHP higher than those to the general population.

In summary, we have conducted extensive experimental studies on phthalates and through the CERHR have evaluated phthalates and BPA. We maintain an objective, science-based approach in dealing with critical issues in toxicology, and we provide sound scientific information on substances of concern to regulatory agencies and the public, contributing to the public health discussions surrounding these important chemicals. Thank you very much for this opportunity to appear today before you. I would be happy to answer your questions.

[The prepared statement of Dr. Bucher follows:]

Testimony
Before the Subcommittee on Commerce, Trade, and Consumer Protection
Committee on Energy and Commerce
United States House of Representatives

National Toxicology Program Determinations on the Health Effects of Bisphenol A and Phthalates

Statement of
John R. Bucher, Ph.D.
Associate Director
National Toxicology Program
National Institute of Environmental Health Sciences
National Institutes of Health
U.S. Department of Health and Human Services

For Release on Delivery
Expected at 10:00 AM
Tuesday, June 10, 2008

Thank you, Mr. Chairman, and good morning. I am Dr. John Bucher, Associate Director of the National Toxicology Program (NTP). The NTP is an interagency program, funded and managed by the National Institute of Environment Health Sciences (NIEHS). NIEHS and NTP are part of the National Institutes of Health, an agency of the Department of Health and Human Services.

The NTP carries out toxicology research and testing on substances of concern to the federal government and the public. We also perform literature review and analysis activities and since 1980 have produced the Report on Carcinogens. In 1998, we established the Center for the Evaluation of Risks to Human Reproduction (CERHR), which carries out literature evaluations on substances that may affect human reproduction and development.

The NTP has extensively researched phthalates for cancer and reproductive effects in animals, and through the CERHR, has reviewed the world's literature on seven phthalates for potential effects on human reproductive health. We have studied bisphenol A (BPA) less extensively in animals, although recently we conducted a lengthy evaluation of the very large literature on the potential for BPA to affect reproduction and development. This evaluation culminates tomorrow with a public peer review of the Draft NTP Brief on Bisphenol A before our NTP Board of Scientific Counselors, a federally -chartered committee of external advisors that provides scientific review for our programs. This draft brief represents our opinion of the science on BPA and is based on our evaluation to date of the literature, informed by the findings of an expert panel and with consideration of public comments solicited on five separate occasions.

BPA is a high-production industrial chemical used to manufacture polycarbonate plastics and epoxy linings of tin cans. It has been known since 1938 to mimic estrogen when given in large amounts to experimental animals. More recently, it has also been studied for its ability at very much lower doses to affect hormonal processes involved in development, when an animal is exposed as a fetus or during infancy. BPA leaches in small amounts from plastic items such as polycarbonate baby bottles and can be measured in infant formula coming from epoxy-lined cans. The 2003-2004 National Health and Nutrition Examination Survey (NHANES III) conducted by the Centers for Disease Control and Prevention (CDC) found detectable levels of bisphenol A in 93% of 2517 urine samples from people six years and older. The CDC NHANES data are considered representative of exposures in the United States.

The scientific evidence that supports a conclusion of "some concern" for exposures in fetuses, infants, and children comes from a number of laboratory animal studies reporting that "low" level exposure to bisphenol A during development can cause changes in behavior and the brain, prostate gland, mammary gland, and the age at which females attain puberty. These studies only provide limited evidence for adverse effects on development, and more research is needed to better understand their implications for human health. However, because these effects in animals occur at bisphenol A exposure levels similar to those experienced by humans, the possibility that bisphenol A may alter human development cannot be dismissed.

Taking this information into account, the NTP reached several preliminary conclusions in our draft brief. We express "some concern" that current estimated exposures of BPA to fetuses, infants, and children could cause neural and behavioral effects, effects on the prostate and mammary gland, and an earlier age at which females attain puberty. We express "negligible

concern" or "minimal concern" that current exposures to BPA could cause adverse health effects in other segments of the population. "Some concern" is the midpoint of a 5 level scale; the levels are negligible concern, minimal concern, some concern, concern, and serious concern.

Although we agreed with our expert panel in expressing "some concern" for current exposures to BPA to produce neural and behavioral effects to fetuses, infants and children, we expressed an elevated level of concern ("some concern") over the conclusions reached by our Expert Panel ("minimal concern") for changes to the prostate as well as earlier puberty in females. The Expert Panel did not specify a level of concern for the mammary gland. These elevated concerns were based on: 1) new literature; 2) clarifications provided in public comments to studies considered of low utility by our Expert Panel; and 3) scientific justification for using data from studies utilizing non oral routes of exposure to neonatal animals.

There are a number of uncertainties in the scientific information on BPA. The literature from experimental animal studies is large, but with many conflicting findings. Moreover, there are insufficient data from studies in humans to determine directly whether BPA is affecting human reproductive health.

The studies on which we base "some concern" have limitations. They are not the traditional safety assessment studies done according to regulatory guidelines. Rather, they are smaller studies carried out in academic labs. These have often examined subtle developmental endpoints in experimental animals that are more difficult to interpret with regard to how they contribute to the weight–of–evidence for human health risks. Despite the limitations of these studies, the NTP determined that because the subtle effects in animals occur at BPA exposure levels similar to those experienced by humans, the possibility that BPA may alter human

development cannot be dismissed. As I mentioned earlier, the NTP Board of Scientific Counselors will review the draft brief at its meeting tomorrow. We will take their recommendations into consideration, and the final brief will be published later this year.

Turning to phthalates, chemicals used to make certain plastics flexible, the NTP has conducted 13 cancer bioassays and 45 studies on reproductive or developmental toxicity with various phthalate esters. The fact that specific phthalates can adversely affect reproduction has been known for more than 25 years, and it is now known is that fetal animals are more sensitive than newborn animals, which in turn are more sensitive than older animals. Since the late 1990s it has been known that certain phthalates specifically affect development of the male reproductive system.

Not all phthalates produce adverse reproductive effects in animal studies. The phthalates that produce adverse reproductive effects are called "active" phthalates. All "active" phthalates cause similar toxicity to the developing rat fetus when exposure occurs during a critical window of sexual differentiation during pregnancy. These agents induce malformations in the male reproductive tract by affecting development that is mediated through androgens (e.g. testosterone). The most severe malformations occur with higher doses. In addition, some phthalates, when administered to the developing fetus, can also induce subsequent testicular tumors in the adult animal after being exposed only during the short window of pregnancy.

In humans, a few small studies have linked maternal exposure to specific phthalates with adverse outcomes in their children, including decreased testosterone levels in boys. However, concerns remain about the assessment of confounding and contamination by breast pump use. Thus, additional research is needed to confirm these findings.

Failure of normal development of the testis has been proposed to explain increases in human male reproductive problems. However, thus far, no cause and effect relationship has been established between any environmental agent and these human outcomes.

As mentioned earlier, the NTP CERHR has reviewed the literature on phthalates. We recently updated the review for one phthalate, di(2-ethylhexyl)phthalate (DEHP). DEHP is used as a plasticizer of polyvinyl chloride in the manufacture of a variety of consumer products and medical devices.

The NTP expressed "serious concern" for male infants for whom exposure to DEHP during certain medical treatments could adversely affect development of the reproductive tract. We expressed "concern" for male offspring of women undergoing certain medical treatments during pregnancy or breastfeeding, and for infants less than one year old exposed to DEHP from diet or mouthing of DEHP-containing objects, or undergoing certain medical treatments. We expressed "some concern" for male children who may be exposed to levels of DEHP higher than those to the general population.

In summary, the NTP has conducted extensive experimental studies on phthalates and has conducted CERHR evaluations of phthalates and BPA. NTP maintains an objective, science-based approach in dealing with critical issues in toxicology and provides sound scientific information on substances of concern to regulatory agencies and the public, contributing to the public health discussions surrounding these important chemicals.

Thank you for this opportunity to appear before you today to provide this statement. I will be happy to answer any questions you may have.

One Page Summary of NIEHS Testimony by John Bucher, Associate Director NTP
Subcommittee on Commerce, Trade & Consumer Protection
U.S. House of Representatives Committee on Energy & Commerce
10 June 2008

I am Dr. John Bucher, Associate Director of the National Toxicology Program (NTP). The NTP has researched phthalates for cancer and reproductive effects in experimental animals, and our Center for the Evaluation of Risks to Human Reproduction (CERHR) has reviewed the literature on seven phthalates and on bisphenol A (BPA) for potential effects on human reproductive health.

BPA has been extensively studied for its ability at very low doses to affect hormonal processes involved in development. The doses of BPA that cause subtle effects on the development of animals are close to estimates of current exposures to the U.S. population.

Based on these animal studies, the NTP CERHR express "some concern" that current exposures of BPA to fetuses, infants, and children could cause neural and behavioral effects, effects on the prostate and mammary gland, and an earlier age at which females attain puberty, and "negligible concern" or "minimal concern" for effects in other segments of the population.

The NTP has conducted many experimental animal studies on various phthalate esters. Not all phthalates produce adverse reproductive effects, but all "active" phthalates cause malformations or cancer in the male reproductive tract of animals exposed during development.

The NTP CERHR expressed "serious concern" that current exposures of male infants to one particular phthalate, di(2-ethylhexyl)phthalate (DEHP), during certain medical treatments could adversely affect development of the reproductive tract. We expressed "concern" for male offspring of women undergoing certain medical treatments during pregnancy or breastfeeding, and for infants less than one year old exposed to DEHP from diet or mouthing of DEHP-containing objects, or undergoing certain medical treatments. We expressed "some concern" for male children who may be exposed to levels of DEHP higher than those to the general population.

Ms. SCHAKOWSKY. Dr. Alderson.

STATEMENT OF NORRIS ALDERSON, PH.D., ASSOCIATE COMMISSIONER FOR SCIENCE, FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES, ROCKVILLE, MARYLAND

Dr. ALDERSON. Good morning, Madam Chair, and members of the subcommittee. I am Norris Alderson, Associate Commissioner for Science at the FDA. Thank you for providing an opportunity to discuss FDA's ongoing work regarding the safety of bisphenol-A. This past April, FDA Commissioner Dr. von Eschenbach, formed an agency-wide BPA task force, which I chair, to conduct a review of the concerns raised in a recent review of the literature on the safety of BPA. The task force is undertaking a cross agency look at the current research and information on the safety of BPA. Although our review is ongoing, at this time we have no reason to recommend that consumers stop using products containing BPA.

A large body of evidence indicates that currently marketed products containing BPA such as baby bottles and food containers are safe, and that exposure levels to BPA from these products are well below those that may cause health effects. I also want to emphasize that research on the safety of BPA is a very active area. If FDA's review leads us to a determination that the use of BPA is not safe, we will not hesitate to take action to protect the public health. I also want to note that at FDA's request a subcommittee of the FDA science board will review our task force report on the safety of BPA and will hold a public meeting on the topic later this year. The science board, which is an independent advisory body to FDA, will receive the findings of the subcommittee during its fall meeting.

Bisphenol-A is used in the manufacture of two types of polymers used in food contact articles. Polycarbonate plastics are used in products such as water and infant bottles, while epoxy-based enamels and coatings are widely used as inner linings for food and beverage cans. These food contact substances have been regulated by FDA for many years. Small residual amounts of trace BPA can remain in polymers and may migrate to food during the use of the product. For this reason, FDA's safety assessments include a consideration of likely consumer exposure. We have determined that dietary exposure to BPA from these uses is in the very low parts per billion range. The task force is looking at all products we regulate to get a better understanding of the total exposure.

We are already focusing on the specific concerns raised by the reports that Dr. Bucher just talked about. In November of 2007, the NTP Center for Evaluation of Risks to Human Reproduction released its expert panel report which stated that there are minimal concerns for BPA exposure to pregnant women, fetuses, infants, and children. The NTP draft report later in April of this year reiterated that panel's conclusions but upgraded some of those concerns. These analyses included relatively new data and emerging or difficult to interpret endpoints in toxicology, and considered the fact that the studies currently available provide limited evidence and contain numerous uncertainties.

FDA has carefully studied the report and conclusions of the NTP's expert panel, and we are actively reviewing the NTP task force report. Also, FDA's National Center for Toxicological Research in Jefferson, Arkansas is discussing with the NTP additional research needs relating to BPA. Neural and behavior development effects were also the focus of a recent draft risk assessment released by Health Canada and Environment Canada in April. FDA has been discussing this report with our Canadian counterparts. The NTP draft brief and the Canadian draft risk assessment both suggest that more research is needed. FDA itself began a formal risk reassessment of BPA in early 2007. FDA's initial reevaluation of BPA safety focused on possible low dose effects, and we concluded that the current level of exposure to adults and infants is safe.

This conclusion was based on a review of the most relevant data, including our reviews completed in July, 2007, on two pivotal multi-generational studies. FDA's findings thus far are supported by the conclusions of two risk assessments conducted by the European Food Safety Authority and the Japanese National Institute of Advanced Industrial Science and Technology. Let me briefly mention phthalates, which are also a concern to this subcommittee. The BPA task force is also compiling a comprehensive inventory of FDA products that contain phthalates. FDA, primarily through NCTR, is conducting research to broaden our understanding of potential health risks posed by exposure to phthalates.

In conclusion, let me emphasize that current evidence indicates that BPA exposure from food contact materials is well below the levels that may cause health effects, but FDA's conclusions on the safety of the products it regulates are never set in stone. They are always subject to review or revision when new data or better analyses become available. At the end of the day, FDA's goal is always to act within our authority to protect the public health. Thank you for the opportunity to testify today. I will be happy to answer any of your questions.

[The prepared statement of Dr. Alderson follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

STATEMENT OF

NORRIS ALDERSON, PH.D.

ASSOCIATE COMMISSIONER FOR SCIENCE

FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON COMMERCE, TRADE AND

CONSUMER PROTECTION

COMMITTEE ON ENERGY AND COMMERCE

U.S. HOUSE OF REPRESENTATIVES

JUNE 10, 2008

INTRODUCTION

Good morning, Chairman Rush and Members of the Subcommittee. I am Dr. Norris Alderson, Associate Commissioner for Science at the U.S. Food and Drug Administration (FDA or the Agency), part of the Department of Health and Human Services (HHS). FDA appreciates the opportunity to discuss our ongoing work regarding the safety of bisphenol A (BPA).

In light of recent reports and statements from the National Toxicology Program (NTP) at the National Institutes of Health, Health Canada, and interested public health advocates, FDA believes it is important that consumers have accurate and up-to-date information about BPA. We have established an Internet page at *http://www.fda.gov/oc/opacom/hottopics/bpa.html*, where consumers can find such information.

On April 17, 2008, FDA Commissioner Andrew von Eschenbach formed an Agency-wide BPA Task Force, which I chair, to conduct a review, encompassing all FDA-regulated product lines, of the concerns raised about BPA. The task force is undertaking a broad review of current research and information on BPA. In addition to looking at the food and beverage containers that have been the focus of recent concerns as well as our regulatory efforts over the years, the task force is conducting an inventory of all products regulated by FDA's food and medical products centers to better understand other potential routes of exposure. We are already looking at the specific concerns raised by NTP in its recent Draft Brief and the draft risk assessment released by Health Canada last month.

At this time, FDA is not recommending that consumers discontinue using food contact materials that contain BPA. Although our review of the NTP reports is continuing, a large body of available evidence indicates that food contact materials containing BPA currently on the market are safe, and that exposure levels to BPA from these materials, including exposure to infants and children, are below those that may cause health effects. We also acknowledge that BPA research is an extremely active area, and we want to assure you that if FDA's review of data leads us to a determination that uses of BPA are not safe, the Agency will take action to protect the public health.

REGULATION OF COMPONENTS OF FOOD CONTACT MATERIALS CONTAINING BPA

BPA is used in the manufacture of two types of polymers used in food contact articles, specifically, polycarbonate polymers and epoxy-based enamels and coatings. These food contact substances have been regulated for many years pursuant to regulations published in Title 21 of the *Code of Federal Regulations* (CFR). Polycarbonate (PC) polymers, which are found in products such as water and infant bottles, are regulated in 21 CFR §177.1580. Epoxy-based enamels and coatings, which are widely used as inner linings for food cans, are regulated in 21 CFR §175.300 (b) (3) (viii), 21 CFR §177.1440 and 21 CFR §177.2280. Because no polymeric reactions go entirely to completion, small residual amounts of BPA can remain in polymers and may migrate into food during use of the product. For this reason, FDA's safety assessments include a consideration of likely consumer exposure, which I will describe shortly. From these assessments, the Agency has determined that dietary exposure to

BPA from these uses is in the very low parts per billion range, which is well below the levels that would cause adverse health effects. Further, it is important to emphasize that as new data and reviews of BPA have become available, FDA's review of the safety of BPA has been an ongoing process.

EVALUATION OF BPA SAFETY

Although FDA has been actively surveying data on BPA for many years, the Agency began a formal reassessment of the chemical in early 2007. This reassessment initially focused on possible "low-dose" effects for BPA but, in the fall of 2007, we added an evaluation of the endpoints identified by an expert panel of the NTP's Center for the Evaluation of Risks to Human Reproduction (CERHR) after the CERHR meeting in August 2007.

In evaluating the safety of food contact articles or their constituents, such as BPA, FDA's safety assessment relies on evaluating probable consumer exposure as a result of the proposed use and other authorized uses, and ensuring that the probable consumer exposures are supported by the available toxicological information. With regard to consumer exposure, FDA found that the small amounts of BPA that migrated into food from the use of PC-based polymers and BPA-based epoxy coatings result in a cumulative daily intake for adults of 11 micrograms per person per day (μg/person/day).

This estimate is based on: 1) the migration levels of BPA into food, or into food-simulating solvents, under the most severe conditions of use (i.e., time and temperature), and 2)

information on the types of food contacted, the fraction of the diet that would come into contact with that type of food contact material, and whether the finished food contact article would be intended for single or repeated use. FDA's evaluation also considered that the use of can enamels in infant formula packaging and the use of PC baby bottles results in an estimated daily intake of 7 μg/infant/day. These estimates relied on data generated by FDA laboratories or the regulated industry, or available in the open literature, on BPA levels in canned food and in food contacting PC articles.

In conducting this evaluation, FDA was aware that higher migration levels had been reported in some studies available in the literature. Many of those studies were conducted under very unrealistic conditions, such as the use of aggressive solvents or extremely high temperatures that are not reflective of how the products were intended to be used by consumers. Those studies were deemed to not be representative of actual use conditions. In our evaluation of consumer exposure, we used exposure assumptions that while based on realistic scenarios, tended to over-estimate consumer exposure.

FDA's reassessment of possible "low-dose" effects of BPA concluded that the current level of exposure to adults and infants is safe as defined in 21 CFR §170.3(i). This conclusion was based on our review of the most relevant data available at that time, including our analyses, completed in July 2007, of two pivotal multi-generational oral studies performed under applicable regulatory guidelines. The studies included the examination of reproductive and some developmental endpoints and a large range of exposures, including low doses. These

studies include a two-generation reproductive toxicity test in mice and a three-generation reproductive toxicity test in rats.

These studies were considered pivotal in our review of the existing data for a number of reasons. These include: 1) they were conducted in a manner that FDA would recommend to a stakeholder seeking an approval for a new use (i.e., they follow recommended guidelines) including extended parameters allowing for the examination of issues that were controversial to BPA at the time; 2) they were submitted to the Agency with supporting information (raw data) allowing for our independent evaluation of the findings; and 3) they both included a large range of exposures, including a range of high and low doses which allowed for the examination of dose response curves. With regard to FDA's evaluation of BPA, these studies are often given more weight than publications in the public literature that examine the same endpoints because the publications often lack details and supporting data that would be necessary for an independent evaluation of the underlying data by Agency scientists. In addition, many of the published studies on BPA have numerous protocol limitations, including the animal model utilized, the method of BPA measurement, the statistical analysis of the data, the lack of multiple/correctly spaced doses in the experimental protocol, and the route of administration.

By comparing the "no observed effect" level (5 milligrams per kilogram of body weight per day) derived from the reproductive and developmental endpoints examined in these pivotal studies to the estimated daily intake of BPA, FDA determined that an adequate margin of exposure exists to reach a conclusion of "reasonable certainty of no harm under the intended

conditions of use," the standard set forth in 21 CFR §170.3(i). That margin of exposure is approximately 7,000 fold for infants -- that is, the levels of exposure to BPA at which any effects would be observed in infants is about 7,000 times higher than our estimates of actual exposure.

In addition, FDA has completed a summary of the pharmacokinetic data on BPA in multiple species. FDA has determined that understanding the species differences and the differences in how metabolic systems handle BPA administered via various routes of exposure, such as oral versus subcutaneous, are also pivotal to examining the safety of BPA.

FDA's findings thus far are underscored by the conclusions of two risk assessments for BPA from 2006, conducted by the European Food Safety Authority's Scientific Panel of Food Additives, Flavourings, Processing Aids and Materials in Contact with Food, and the Japanese National Institute of Advanced Industrial Science and Technology. Each of these documents considered the possibility of a low-dose effect and concluded that no health risk exists for BPA at the current exposure level. Neither of these risk assessments disagrees with FDA's current position of the safe use of BPA at the current exposure level.

BPA TASK FORCE REVIEW

FDA has carefully studied the review and conclusions of the expert panel convened by CERHR, released on November 26, 2007. The CERHR expert panel found that, based on current BPA exposure levels, "some concern" exists for pregnant women and fetuses and

infants and children for exposure to BPA causing neural and behavioral effects. The expert panel also concluded that there was "minimal concern" for BPA exposure in these populations for effects in the prostate gland, mammary gland, and an earlier age for puberty in females.

The NTP Draft Brief released on April 14, 2008, reiterated the conclusions of the CERHR panel with regard to neural and behavioral effects. However, the NTP Draft Brief departed from the expert panel in concluding that "some concern" exists for effects in the prostate gland, mammary gland, and an earlier age for puberty in females for BPA exposure to fetuses, infants and children. These analyses emphasized relatively new data and emerging or difficult-to-interpret endpoints in toxicology and considered the fact that the studies currently available provide limited evidence and contain numerous uncertainties. It is noteworthy that the increase in concern from "minimal" to "some" from the conclusion from CERHR's expert panel to NTP's Draft Brief reflects numerous studies that have appeared in the literature only in the past several months. Although the NTP Draft Brief discusses "some concern" for developmental exposure and mammary and prostate gland cancer, it also highlights the uncertainties regarding these data and states that the evidence is not sufficient to conclude that BPA is a rodent carcinogen for these endpoints or that BPA presents a cancer hazard to humans.

Neural and behavior development effects were also the focus of a recent draft risk assessment released by Health Canada and Environment Canada on April 18, 2008. Both the NTP Draft Brief and the Canadian draft risk assessment are reviews of existing and recently developed data. Both discuss animal studies on neural, behavioral, and developmental effects and both

assessments point out that these studies provide only limited evidence for concern for human exposure to BPA. Finally, both suggest that more research is needed to better understand their implications for human health.

FDA has not yet completed its review of concerns raised by the CERHR expert panel last fall or the NTP Draft Brief released last month. Therefore, those concerns are under active consideration by FDA centers and the BPA Task Force, and we will take appropriate action, if warranted, at the completion of our review.

PHTHALATES

Because all of FDA's product centers are represented on the BPA Task Force, Commissioner von Eschenbach has also tasked it with establishing a comprehensive inventory of regulated products that contain phthalates. Phthalates are primarily used as plasticizers in polyvinyl chloride (PVC) and polyvinylidene chloride (PVDC) polymers to increase their flexibility. Di-(2-ethylhexyl) phthalate (DEHP) is perhaps the most thoroughly studied among the phthalates. DEHP has long been used to produce highly flexible versions of PVC and PVDC polymers for a variety of applications, such as in flexible packaging film.

FDA-authorized uses of phthalates include uses in flexible food packaging. Over the past decade, however, such food contact uses have been greatly reduced or eliminated through the replacement of PVC and PVDC polymers with other polymers that do not require plasticizers and by the use of alternative plasticizers in PVC and PVDC. FDA's Center for Food Safety

and Applied Nutrition (CFSAN) has tracked the reductions in use of phthalates in food contact materials as well as the development of new toxicological data.

CFSAN has recently established a Phthalate Task Group (PTG) to review all available use and toxicology information associated with phthalate exposure from food contact use and to better characterize any potential risk from these uses. The primary focus of the PTG will be to determine the most realistic exposure estimation and risk associated with phthalate use in food packaging. The PTG will review and address past studies on phthalates and any new information available. If our review indicates that existing data no longer supports the continued safe use of these materials in food contact material, FDA will take appropriate regulatory action to remove these materials from the marketplace.

There are also significant uses of phthalates in certain medical products, such as intravenous solution bags and medical tubing. FDA's Center for Devices and Radiological Health (CDRH) has looked into the use of polyvinyl chloride using DEHP as a plasticizer in medical devices. DEHP is a chemical ingredient that affords PVC many of the physical properties that make it optimally suited for use in many of today's medical devices.

While toxic and carcinogenic effects of DEHP have been demonstrated in laboratory animals, there are no studies in humans that are adequate to serve as the basis for regulatory decision-making. Further, health care providers should not avoid performing certain medical procedures simply because of the possibility of health risks associated with DEHP exposure.

In these cases, the risk of not doing a needed procedure is far greater than the risk associated with exposure to DEHP.

Phthalates are also widely used in cosmetics, serving as solvents for fragrances, antifoaming and suspension agents, skin emollients, and plasticizers in nail products. CFSAN's Office of Cosmetics and Colors has conducted laboratory surveys of phthalate levels in marketed cosmetics. The last survey indicated that diethylphthalate (DEP) was the most frequently used phthalate in cosmetics and that nail enamels contained the highest levels of phthalates, primarily dibutylphthalate (DBP). Based on the results of that survey and the toxicity data currently available, FDA does not believe that phthalates in cosmetics pose a health risk. Since the survey was conducted, we have observed that some cosmetic products are being reformulated to remove phthalates. CFSAN is planning a more extensive survey of a larger number of cosmetic products to better determine to what extent cosmetic products contribute to total human exposure to phthalates. We will continue to monitor and evaluate all available data to ensure that phthalate levels in cosmetic products are not a health concern.

FDA, primarily through its' National Center for Toxicological Research (NCTR), is conducting further research to address uncertainties in our understanding of the potential health risk posed by exposure to phthalates. Much of the concern on medical exposures to phthalates is focused on potential reproductive tract effects in male infants in neonatal intensive care units, a population exposed to high levels of DEHP at a sensitive period of development. The NCTR studies are evaluating the metabolism and toxicity of DEHP

following intravenous exposure in infant male nonhuman primates, a model that more closely resembles the human exposure of highest concern.

CONCLUSION

Although the Agency's review of the newly available reports is continuing, a large body of available evidence indicates that currently-marketed food contact materials containing BPA are safe, and that exposure to BPA from food contact materials, including exposures for infants and children, are below the levels that may cause health effects. We are actively reviewing the data on BPA and will continue to consider the relevance of new data and studies as they appear.

In the case of both BPA and phthalates, FDA's work in assessing the safety of products that contain these chemicals is never truly final, and if our continuing review of all available data leads us to a determination that the current levels of exposure are not safe, we will take appropriate action to protect the public health. Thank you for the opportunity to testify today, and I would be happy to answer any questions.

Ms. SCHAKOWSKY. Dr. Gray.

STATEMENT OF L. EARL GRAY, JR., SENIOR REPRODUCTIVE BIOLOGIST AND TOXICOLOGIST, REPRODUCTIVE TOXICOLOGY DIVISION, OFFICE OF RESEARCH AND DEVELOPMENT, ENVIRONMENTAL PROTECTION AGENCY

Dr. GRAY. Good morning, Ms. Chairman, and members of the committee. My name is Earl Gray, and I am a senior reproductive biologist and toxicologist in the Reproductive Toxicology Division in the Office of Research and Development of EPA. The views expressed here in my testimony today represent my personal views as a scientist and do not necessarily reflect the position of the EPA or the Administration. My research at EPA has focused on the effects of chemicals including endocrine disrupters on the cellular and molecular modes of toxicity leading to abnormal reproductive development in rodents, and we have studied a variety of chemicals including phthalates and bisphenol-A.

In these studies, rat mothers are exposed to an individual chemical or a mixture of chemicals during pregnancy, and the offspring are examined after birth to determine if the chemical induced adverse effects. Phthalates are a high production volume chemical used in many consumer products including toys, baby products, pharmaceuticals, cosmetics, personal care products, and medical devices. The phthalates are ubiquitous in our daily environment and most people, including pregnant women and their fetuses, are exposed to multiple phthalates. In rats, some phthalates cause liver cancer, spontaneous abortions, and reproductive tract malformations in male and female rat offspring. The abnormalities seen in the male rat offspring are described as phthalate syndrome. This syndrome is the focus of many regulatory agencies since it occurs at lower dosage levels than other adverse effects.

The phthalate syndrome is manifested by undescended testes, malformations of the penis and internal reproductive tract and shortened ano-genital distance in males. The process that is disrupted is known as sexual differentiation. It is a process common to all mammals including humans. During sexual differentiation, phthalates disrupt testis function reducing fetal androgen levels which in turn causes abnormal male reproductive tract development, and in fact there are a variety of human syndromes associated with disruption of this pathway. Recently concerns have been expressed about the effects of mixtures of phthalates since humans are exposed to multiple phthalates at one time. Studies with rats show that combining phthalates with other phthalates or with pesticides cause cumulative adverse effects. They do not act independently.

A key question is how do the levels of phthalates that affect rats compare with human exposures? In the last few years several studies have shown that although phthalate levels in most humans are low, a small percentage of people are exposed to much higher levels of phthalates, and when one compares the level of phthalate metabolites in human versus rat amniotic fluid, the environment that the fetus develops in, the levels in humans aren't always that different from those in affected rats, thus the margin of exposure is not always as large as one would like. Using the National Toxi-

cology Program scale, my concern about phthalates are that I have serious concern about the potential effect of phthalates in children and women of child-bearing age exposed during medical interventions and concern for exposure to phthalates in all other women and children, women of child-bearing age and children.

Bisphenol-A is a high production volume chemical used in the synthesis of polycarbonate plastics and found in many consumer products, including baby bottles and can liners. The most recent study show that people are exposed to low levels of BPA. The concerns about BPA expressed here are from the National Toxicology Program expert panel final report of 2007, of which I was a member. This report included our independent evaluation of several hundred papers on the reproductive and developmental toxicity of BPA. The NTP BPA expert panel expressed some concern for neural behavior effects of BPA in humans, whereas all other effects were either negligible or minimal concern.

In summary, I have a higher level of concern for some phthalates than for bisphenol-A based upon the consistency of the adverse effects of some phthalates among many laboratories, the relevance of the effects to humans, and the high dose exposures to some people. Thank you, Chairman and members of the subcommittee for the opportunity to discuss EPA's work on phthalates and BPA, and I look forward to answering any questions that you have.

[The prepared statement of Dr. Gray follows:]

WRITTEN TESTIMONY OF

LEON EARL GRAY JR, PhD*
SENIOR REPRODUCTIVE BIOLOGIST AND TOXICOLOGIST
U.S. ENVIRONMENTAL PROTECTION AGENCY
BEFORE THE
COMMITTEE ON ENERGY AND COMMERCE
SUBCOMMITTEE ON COMMERCE, TRADE, AND CONSUMER PROTECTION
UNITED STATES HOUSE OF REPRESENTATIVES
June 10, 2008

Introduction

Good morning, Mr. Chairman and Members of the Subcommittee. My name is Dr. L. Earl Gray Jr., and I am a senior reproductive biologist and toxicologist in the Reproductive Toxicology Division of EPA's National Health and Environmental Effects Research Laboratory in the Office of Research and Development. I have been employed by EPA for almost 30 years. During my tenure I have published more than 180 peer reviewed journal articles and book chapters. My co-authors and I have published in *Nature* and *Science* as well as several other prestigious journals. I have received more than 15 EPA Scientific and Technological Achievement Awards for research publications and two gold and 6 bronze medals from the EPA for my work. I also am listed as a Highly Cited scientist by Citations Indices and my work has been presented at numerous national and international symposia and several legislative hearings held by various governmental agencies.

My research has focused on the effects of chemicals, including endocrine disrupters (EDCs), on the cellular and molecular modes of action leading to abnormal reproductive development in male and female rodents – an acceptable model for predicting potential effects in humans.

*The views presented in my testimony today represent my personal views as a scientist and do not necessarily reflect the position of EPA or the Administration.

Research in my laboratory has included examining the effects of exposure to environmental estrogens, antiestrogens, androgens, antiandrogens, dioxins and polychlorinated biphenyls (PCBs), phthalates, germ cell toxicants and chemicals that inhibit steroid hormone synthesis. The estrogens that we have studied include ethinyl estradiol (found in birth control pills), methoxychlor (a pesticide), and bisphenol A (BPA). In these studies, animals were exposed during critical developmental stages of life in pregnancy (*in utero)* to determine the latent effects later in life. Currently, we are focusing on how mixtures of phthalates and pesticides interact when administered *in utero*.

Data from these studies have been used by the EPA and other regulatory agencies in chemical-specific risk assessments. The findings from our studies on mixtures of phthalates are currently being reviewed, along with those from other studies, by a National Academy of Sciences panel. Later this year, the panel will provide the EPA with recommendations about conducting cumulative risk assessments on the phthalates.

In today's testimony I will discuss phthalates, and their toxicity. Then I will contrast this discussion with one on the toxicity of BPA. Much of what we know about the toxicity of these chemicals is based on studies that have been conducted in laboratory studies using animal models. Studies using laboratory animal models, when well-conducted by well-accepted standards, can provide valuable information for use in hazard assessments to predict potential toxicity in humans. Both phthalates and BPA produce toxicity by mechanisms that interfere with the endocrine or hormone system. Many pathways in the endocrine system are very similar across species and, therefore, there is strong concern about the potential hazard to humans from any chemical that interferes with hormones. However, the levels of exposure that are needed to elicit toxicity are also critical.

Phthalates

Phthalates are a high-production-volume class of chemicals that are used in many consumer products including toys, baby products and lotions, cosmetics, personal care products, fragrances, air fresheners, medical tubing and devices, blood bags, PVC pipe and flooring, pharmaceuticals, and automobile parts. They are ubiquitous in our daily environment and most people, including pregnant women and their fetuses, are exposed to multiple phthalates at a time.

Several studies have shown that although phthalate exposures in humans are generally low -- basically near the limit of detection -- a small percentage of people are exposed to higher levels of phthalates. This information is based on the level of phthalate metabolites identified in the urine of some pregnant women [1] and in human amniotic fluid [2]. In rats, at certain levels of exposure, phthalates can cause liver cancer[3], spontaneous abortions [4], and reproductive tract malformations in male and female offspring. The adverse[a] reproductive effects seen in the male offspring, described as the "Phthalate Syndrome," are currently the focus of regulatory agencies since this syndrome occurs at lower dosage levels than other toxicities.

[a] **adverse effect**: change in morphology, physiology, growth, development, or life span of an organism, which results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other environmental influences

Although there are literally thousands of studies on phthalates, the Phthalate Syndrome in male rats was not described until 1999 and these studies focused on only a few of the phthalates. The effects of phthalates on female offspring, which include partial to complete absence of the uterus, are only mentioned in one sentence in two papers, one from my laboratory [5] and the other from Dr. Paul Foster's laboratory [6], currently of the NIEHS, NTP. The limited data that are available indicate that Phthalate Syndrome can be induced by phthalate diesters with linear side chains of 4-6 carbons on adjacent side chains and not with phthalate diesters with shorter or longer linear side chains. Thus not all phthalates have equal toxicity.

Mode of Action of Active Phthalate Diesters

Phthalates act by inhibiting fetal rat testis function during a critical stage of life *in utero*. This results in reduced androgen (male hormone) and other hormone levels, hormones that are necessary for normal development of the male reproductive tract. Male offspring exposed to high doses of phthalates *in utero* often display undescended testes and malformations of the penis and internal reproductive tract. This disrupted process in rats, known as sexual differentiation, is common to all mammals and disruption of this pathway in human males also causes profound abnormalities[7].

The levels of the monoester metabolites of dibutyl- (DBP) and diethylhexyl- (DEHP) phthalate measured in the amniotic fluid of rats during sexual differentiation [8], from pregnant rats treated with dosage levels that produce low incidence of statistically significant adverse reproductive effects in male rat offspring, are only about 5 fold (DBP [9]) and 24 fold (DEHP [10]) higher, respectively, than the highest levels of the same metabolites seen in the amniotic fluid from a study of 54 women [2].

This indicates that the margin of exposure (MOE [b]) is not as great as one would generally like. In addition, the scientific literature is consistent in indicating that phthalates show adverse effects in offspring that are produced by disrupting a hormonal signaling pathway common to all mammals including humans.

It is worth noting that there is considerable agreement in the scientific community about the mode of action of phthalates on the fetal male rat. Studies from industry, government and academic laboratories have all found similar effects. Some of the same laboratories reporting adverse effects of phthalates [5,6,11-14] on reproductive development have, in contrast, not detected any low-dose effects caused by BPA[15,16].

[b] **margin of exposure**: ratio of the no-observed-adverse- effect level (NOAEL) to the estimated exposure dose in humans

Phthalate Mixtures

Since most humans are exposed to multiple phthalates, it is critical to understand the biological effects of mixtures of phthalates. Studies in rats show that combining phthalates with other phthalates[13,14] or with pesticides [14,17] can produce cumulative, additive, adverse effects. They do not act independently. The following table describes the relative potencies of several phthalates compared to di(n)ethylhexyl phthalate (DEHP). The estimated potencies describe the potential of each phthalate to disrupt testicular function and/or produce malformations in male rat offspring.

Phthalate	DEHP diethyl hexyl-	DBP dibutyl-	DiBP di-iso butyl-	BBP benzyl Butyl-	DINP di-iso nonyl-	DPP dipentyl-	DEP diethyl-	DMP dimethy-	DOtP dioctyl- ter-
Estimated Relative Potency	1	1	1	1	0.15	3	0	0	0
Reference	13,14,18	6,13,14	14,19	12,14,17,18	18,20	14,21	18	18	18,22

Concerns about Phthalates

Following the scale used by the National Toxicology Program's Center for Evaluation of Risks to Human Reproduction (NTP CERHR) (scale: negligible, minimal, some concern, concern, serious concern) I have "serious concern" about the potential effects in children exposed to phthalates from medical interventions[23,24] where serum levels can reach parts per million concentrations[24] and "concern" for exposure to children and women of childbearing age since the currently available data[1,2,8-10,25] indicate that the margin of exposure can be low for the most highly exposed individuals.

- The mode of action is highly conserved, being common among mammals, including humans,
- While most of the human population appears to be exposed to low levels of phthalate metabolites, some individuals are exposed to very high levels,
- Humans are exposed to multiple phthalates and mixtures of phthalates that have cumulative effects in rats, and
- Effects have been reported in humans in several epidemiology studies including one which reported an association between higher levels of maternal phthalates and reduced anogenital distance (AGD) in male infants (Swan et al., 2005). Shortened AGD is considered an index of demasculinization in rats.

Bisphenol A (BPA)

BPA is a high-production-volume chemical used in the synthesis of polycarbonate plastics and found in many consumer products including baby bottles and can liners. Studies show that most people are exposed to low levels of BPA [26].

My comments about Bisphenol A are based on my participation on the National Toxicology Program's Center for Evaluation of Risks to Human Reproduction Expert Panel (Final Report, Nov 2007[c]) where we evaluated several hundred papers on the reproductive toxicity of BPA. In addition, I have conducted research in my own laboratory on BPA[16,27] and other environmental estrogens [16 28]

[c] http://cerhr.niehs.nih.gov/chemicals/bisphenol/BPAFinalEPVF112607.pdf

National Toxicology Program's Center for Evaluation of Risks to Human Reproduction Panel on BPA. (http://cerhr.niehs.nih.gov/)

In 2006, the National Toxicology Program's (NTP) Center for Evaluation of Risks to Human Reproduction (CERHR) formed the BPA Expert Panel with experts in the fields of statistics, epidemiology, reproductive and developmental toxicology and exposure. The Panel included several internationally known scientists, some of whom have worked on BPA. A search for citations on the National Library of Medicine Pub Med database on scientific publications reveals that this group has well over 700 scientific publications in the fields mentioned earlier.

The literature on BPA is quite unique in two respects. First, there is no lack of data for such a review. There were over 700 studies considered by our Expert Panel and more are published every day. Secondly, the results of the studies on the low dose effects of BPA are mixed. In

general, studies that have examined common endpoints after exposure to BPA during development have not produced consistent results.

The Panel independently developed criteria to rate the quality of the studies. We reviewed studies published in the scientific literature and reports, established levels of concern for potential adverse effects of low doses of BPA in humans, and wrote draft and final reports. Early on, a contractor who had routinely assimilated all of the scientific studies and prepared a draft summary for all the chemicals that had been reviewed by CERHR panels was dismissed from the process for reviewing BPA. However, neither the contractor nor the CERHR staff influenced our decisions. The Panel reviewed all constructive comments submitted to the NTP through their public comment period and adjusted our assessment as warranted.

At the first face-to-face meeting of the Panel, reproductive and developmental toxicologists as a group developed criteria for inclusion of papers in the final report. The criteria provided minimum standards for experimental design and statistical analysis. Many studies failed to meet these minimal criteria – these studies came from industry, government and academic laboratories. One of the most common deficiencies was failure to control for and statistically account for "litter effects," an error that can result in random variation being identified as a low dose effect of BPA [29,30]. We also omitted studies from review that used a positive control group of animals that did not show any adverse effects, studies that injected BPA into the brain or spinal cord, and studies that did not have a concurrent control group of animals.

In our evaluations we never considered the sources of funding or where the investigators were employed. In our initial evaluation of study quality we also did not consider who the investigator was or if the study detected low-dose effects or not. We were evaluating only the

experimental designs and statistical methods to ensure that our report would be based only on high quality studies. Studies that did not meet these criteria were deemed "inadequate" for inclusion in the final report.

Unlike phthalates, which have also been reviewed by panels of independent experts convened by CERHR, the literature has not led to a scientific consensus on the reproductive effects of low doses of BPA in any rodent species. Also, in contrast to the phthalates, there currently is no evidence of high-level exposures to BPA *in utero* or to children. Most of the "low dose" studies that have been conducted in rodent models appear to be using BPA levels that are several orders of magnitude higher than human exposures.

Why is there so much controversy about the low dose effects of BPA?

In my opinion, the controversy exists because:

- Many of the low dose effects of BPA in rodents are not robust and have not, or cannot be reproduced across multiple laboratories. Effects need to be robust and reproducible.
- The low dose **effects** are frequently not **adverse** effects.
- None of the studies reporting effects at low doses have included a sufficient number of dosage levels to enable researchers to link the effects with adverse effects and many do not include any functional assessment of the reproductive system at all. These low dose effects must be causally linked to adverse effects to be useful in a risk assessment.
- If we assume that these low dose effects are "real," then why aren't there effects at high dosage levels in multigenerational studies? Every other EDC studied in this manner produces a continuum of effects across the dose-response curve, including all other estrogens, and although the effect at low doses can differ from that at high doses the high doses result in adverse changes in reproductive function.

Many "effects" in the "low dose" BPA studies such as cancer, reproductive tract malformations and infertility, have never been causally linked to BPA administration.

Currently, there is no proven biological mode of action for the low-dose effects reported for BPA. We do not know what pathway might be disrupted in rodents and whether it is conserved in humans or whether these "effects" are unique to rodents. For example, around the time of birth estrogens have a very important role in masculinizing the brain of the male rat whereas this pathway is generally assumed to be much less important in human males where the androgen signaling pathway predominates.

BPA is an estrogen mimic, displaying estrogenic activity *in vitro* and in short-term *in vivo* Estrogen Receptor (ER) alpha and beta-dependent assays. However, BPA is about 10,000 fold less potent than estradiol, an important human estrogen. The nuclear ER alpha receptor is the most important mode of action for estrogens in the reproductive tract. Based on the low levels of human exposure to BPA, this mode of action would not likely be activated at very low dose levels. Genomic studies in rodents do not detect activation of estrogen-dependent genes after exposure to low dose levels of BPA, indicating the ER signaling pathway is only induced at moderate to high dose levels in the rat uterus or fetal rat testis [29,31].

To explain many of the low-dose effects, BPA would have to be as potent as the most potent estrogens such as estradiol 17β, ethinyl estradiol and diethylstilbestrol (DES). Note that all of these estrogens produce obvious adverse reproductive effects at higher dosage levels. Such a remarkable proposition requires remarkable proof, and the database does not provide this level of

proof. Hence the present controversy in the scientific community about the low dose effects of BPA.

The CERHR Expert Panel had different levels of concern for the low-dose effects of BPA on humans for different endpoints. These are presented in the attached appendix.

- Overall, the Panel's highest level of concern was ***"Some Concern"*** for neural and behavioral effects of BPA on humans. However, these studies did not reveal a clear pattern of behavioral or neural alterations or disruption of a single neural pathway. My opinion is that this indicates an obvious need for more research. All other effects were determined to be of either negligible or minimal concern.

Summary

In summary, I have different levels of concern for these two classes of EDCs, with a higher level of concern for some phthalates than for BPA.

- **Phthalates**
  - ***Concern*** [c] for children and women of child-bearing age and
  - ***Serious Concern*** [d] for children and pregnant exposed to phthalates by medical interventions

[c] This level of concern is one level higher than that expressed in the 2006 NTP Monograph on DEHP[10]. because I considered a) that people are exposed to multiple phthalates, not just DEHP, and b) that new data have shown that some people are exposed to very higher levels of phthalates than previously reported.

[d] This level of concern are the same as that expressed in the 2006 NTP Monograph on DEHP[10].

- **BPA** [e]
  - -***Some Concern*** for neural and behavioral effects and
  - -***Minimal to Negligible Concern*** for other effects

[e] These levels of concern are compared to those expressed in the NTP Draft Brief in Table 1

The difference in levels of concern expressed here for some phthalates as opposed to BPA is based upon the fact that:

1. Several publications indicate that some women and children are exposed to high levels of phthalates, levels are only 5- and 24-fold lower than levels seen in rats displaying statistically significant incidences of adverse reproductive effects, thereby providing a small margin of exposure [1,2,8-10,25], and
2. The consistency of the scientific literature on the phthalates showing adverse effects in offspring produced by disruption of a hormonal signaling pathway common to all mammals including humans.

Thank you, Chairman Rush and members of the Subcommittee for this opportunity to discuss EPA's work on phthalates and BPA. I look forward to answering any questions you may have.

LE Gray Jr's comparison of CERHR BPA Expert Panel's (2007) levels of concern for the potential of "low doses" of BPA to produce adverse effects in humans with the levels of concern in the NTP draft Brief (2008)			
Effect	**Expert Panel Report Level of concern (Section 5)**	**NTP Draft Brief Level of concern**	**Difference**
Neural and behavioral effects in fetuses, infants and children	**Some**	**Agreed**	**None**
Age at puberty in females	**Minimal**	**Some**	**NTP higher**
Prostate gland "lesions" – PIN	**Minimal**	**Some**	**NTP higher**
Tissue changes ("lesions") in mammary gland	**Negligible**	**Some**	**NTP higher**
Fetal or neonatal mortality	**Negligible**	**Agreed**	**None**
Birth weight or growth of offspring	**Negligible**	**Agreed**	**None**
Reproductive effects in non-occupationally exposed adults (including fertility, hormone levels and sperm numbers)	**Negligible**	**Agreed**	**None**
Reproductive effects in occupationally exposed adults	**Minimal**	**Agreed**	**None**
Malformation in offspring or fetuses	**Negligible**	**Agreed**	**None**
Effect	**Expert Panel Report Level of concern (Section 3)**	**NTP Draft Brief Level of concern**	**Difference**
Fertility in offspring	**Negligible**	**Unclear**	**None**
Hormone levels in offspring	**Literature on low dose studies in inconsistent and insufficient to reach a conclusion**	**Same**	**None**
Sperm numbers with developmental exposure in offspring	**Literature on low dose studies in inconsistent and insufficient to reach a conclusion**	**Same**	**None**

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Ms. SCHAKOWSKY. I want to thank the witnesses for their testimony, and we will begin the questioning now. I will begin with that questioning for 5 minutes. I wanted to ask Dr. Babich, there seems at least to me to be some confusion in the media and even in some testimony, are there phthalates in teethers, rattles, and pacifiers, and, if so, which phthalate?

Dr. BABICH. In 2002 there were no phthalates in teethers, rattles, or pacifiers.

Ms. SCHAKOWSKY. Do you know that because CPSC actually tested it?

Dr. BABICH. In 2002, we tested teethers, rattles, soft plastic toys, the kinds of products that children mouth, and there were no phthalates in teethers, rattles, and of course pacifiers, and about 40 percent of the soft plastic toys contained DINP. There were for the most part very few that had phthalates. Some had phthalate substitutes.

Ms. SCHAKOWSKY. So there was a voluntary agreement in which the industry agreed to exclude DEHP and DINP from toys also. What percentage did you say was still present in toys?

Dr. BABICH. Well, in 2002 the soft plastic toys, which were not part of the agreement, 40 percent of them had DINP.

Ms. SCHAKOWSKY. They were not part of the——

Dr. BABICH. Not part of the agreement applied to teethers, rattles, and pacifiers.

Ms. SCHAKOWSKY. Do foreign manufacturers comply with these voluntary agreements?

Dr. BABICH. In 2002, we surveyed pretty much everything we could get our hands on, and that is what we found.

Ms. SCHAKOWSKY. And so there is no ongoing——

Dr. BABICH. So, yes, I would say that as far as we know they do comply.

Ms. SCHAKOWSKY. OK. And there is no ongoing testing or——

Dr. BABICH. Not at the moment, no.

Ms. SCHAKOWSKY. But unlike the FDA, the CPSC doesn't have pre-market approval of chemicals, is that correct?

Dr. BABICH. True.

Ms. SCHAKOWSKY. That is true. Dr. Bucher, in your testimony you referred to active phthalates. I wondered if you could expand on that, which phthalates are considered active and why, what makes them active?

Dr. BUCHER. Well, there are certain phthalates based on their structure that when metabolized break down to common toxic intermediates, and both Dr. Gray and Dr. Foster, who is accompanying me, are world experts on phthalates and probably would be better to address this issue, but when I mentioned active phthalates it is those that are toxic as opposed to those classes of phthalates that are in fact not toxic.

Ms. SCHAKOWSKY. Did you want to comment on that then, Dr. Gray?

Dr. GRAY. Yes. I agree with Dr. Bucher's comments. Some phthalates have no activity in inhibiting fetal rat testosterone synthesis and others are active in this assay. It is determined by the structure activity, and the interesting structure activity for the fetal effects is similar to that seen for the testicular effects in the

pubertal male rats. In the written testimony we provided, we tried to include a table of a few of the phthalates that we have examined and the relative potencies for their ability to either inhibit fetal testosterone or cause reproductive tract malformations in the male.

Ms. SCHAKOWSKY. So the active ones that were banned by the EU?

Dr. GRAY. Not entirely, no. There were three phthalates in one category that included DEHP, DBP, and BBP, and those are active. There are several other phthalates that have this reproductive toxicity that are not included in the EU list. Some of them we have found to be more potent than those 3.

Ms. SCHAKOWSKY. I wanted to understand why you selected the particular nine phthalates that you did for conducting your research. You did not include—did you include DIDP or DNOP?

Dr. GRAY. We have not done more phthalates. We would like to look at more phthalates though. It is just a question of time and resources. We have just started doing these structure activity correlations on fetal androgen levels in the last couple of years so there are several more we would like to look at. The DNOP, you could be referring to a different structural formulation, so we have looked at the di-ethylhexyl terth ally, which has a structure similar to DEHP and it is inactive because the chains are in a different position on the ring, so there are a large number of phthalates that we have not looked at.

Ms. SCHAKOWSKY. The point is that they are still on your agenda to look at?

Dr. GRAY. Yes, until I retire.

Ms. SCHAKOWSKY. OK. After 30 years already, right?

Dr. GRAY. Oh, but it is fun.

Ms. SCHAKOWSKY. OK. Mr. Whitfield.

Mr. WHITFIELD. Thank you, Madam Chairman, and thank you all for taking time to be with us today, and we appreciate your testimony very much. Just to make sure I understand all this. Right now there are no phthalates in any teething or rattles that children might put in their mouth, is that correct?

Dr. BABICH. Right now there are no phthalates in teethers, rattles, or pacifiers but they can be in other kinds of children's products.

Mr. WHITFIELD. But in that category the manufacturers voluntarily removed it, is that correct?

Dr. BABICH. Voluntarily removed it.

Mr. WHITFIELD. And then if we look at all other toys with phthalates 40 percent of all other toys would have phthalates in them.

Dr. BABICH. Right. That is based on our 2002 data, yes.

Mr. WHITFIELD. OK. Now, Dr. Gray, I noticed when you testified you said that you were not testifying on behalf of EPA but you were testifying personally today, is that correct?

Dr. GRAY. That is correct, as a scientist.

Mr. WHITFIELD. Now what about the other 3, are you all testifying for your agencies or are you testifying personally? You are testifying for your agencies? Now why did EPA not want to testify as an agency today?

Dr. GRAY. Well, my understanding was that there was a request for me to come to present the scientific issues on the phthalates and bisphenol-A and not on the policy, so I can't handle policy questions but I can answer scientific questions in more detail than——

Mr. WHITFIELD. Does the EPA have a policy on these two chemicals?

Dr. GRAY. They have regulatory action ongoing. They have begun risk assessments on some of the phthalates in ORD, and those are planned in OPTS on completion of the National Academy of Sciences Committee review on the cumulative effects of phthalates.

Mr. WHITFIELD. OK.

Dr. GRAY. And I know that they plan to look into a risk assessment on bisphenol-A, I think when the NTP has released its final report on bisphenol-A.

Mr. WHITFIELD. Now the European Union was the first governmental entity that banned any phthalates, is that correct?

Dr. GRAY. I believe so.

Dr. BABICH. I believe so.

Mr. WHITFIELD. And what year was that?

Dr. BABICH. I am not certain of the exact year. They had a temporary ban around '98, '99, and then a couple of years ago it was sort of finalized.

Mr. WHITFIELD. OK.

Dr. BABICH. I could check the exact dates.

Mr. WHITFIELD. Now have you all had an opportunity to review the scientific data on which they made their decision?

Dr. BABICH. Well, in fact, we worked with the various European scientists during the entire process because we realized that it is an international problem that we all faced. We also after all the work was completed, we had a series of teleconferences with the European scientists to discuss whatever the differences may be. Now we looked at only one phthalate, DINP, because that is all that was being used. As far as that one phthalate goes, we decided that on a scientific level we were virtually 100 percent in agreement.

Mr. WHITFIELD. On that one.

Dr. BABICH. On the scientific issues relating to that one phthalate.

Mr. WHITFIELD. And what was that conclusion?

Dr. BABICH. Well, that exposure from these products was too low to present a hazard.

Mr. WHITFIELD. And the Europeans agreed with that as well?

Dr. BABICH. The European scientists agreed with that as well.

Mr. WHITFIELD. Then why did they ban all six or seven of these?

Dr. BABICH. Their regulatory process is very different from ours. In the U.S. we have regulatory agencies that issue regulations. In the EU, they are not regulations. They have legislation, so it is a different process.

Mr. WHITFIELD. OK. Now you all are regulators, and I know on the second panel we are going to have—you are not regulators? The agencies are involved in regulation, FDA.

Dr. BABICH. I am involved in regulation.

Mr. WHITFIELD. Are you aware of any substitutes that can readily be used for phthalates? I know that there is this—are there available substitutes?

Dr. BABICH. Well, we have been trying to compile a list. There are several that were used back in 1999 when they voluntarily took out the phthalates from some products, and there is a long list of substitutes, but as far as we can tell none of them is as well studied as the phthalates, and for some of them we could find little or even no data.

Mr. WHITFIELD. So that is of concern.

Dr. BABICH. Well, that is a concern to us, and in fact we are starting to look at the toxicity, just beginning to look at the toxicity of the phthalate substitutes.

Mr. WHITFIELD. I see my time has expired, Madam Chair.

Ms. SCHAKOWSKY. OK. Next, the gentlewoman from Colorado, Ms. DeGette. Oh. Thank you. Ms. Hooley from Oregon.

Ms. HOOLEY. Thank you, Madam Chair. I have a series of questions. Dr. Gray, animals exposed to the phthalates have shown serious health problems such as liver cancer, kidney cancer, male reproductive organ damage, but have any studies shown that phthalates cause health problems in humans? We know what happens in animals, but what about humans?

Dr. GRAY. Well, there are a variety of epidemiological studies that have reported associations between health effects in humans and phthalate exposures. And I submitted a list of those in the briefing package. It is included with the written testimony. They show a correlation between levels and effect so they are not causal associations.

Ms. HOOLEY. Are phthalates, this is for Dr. Gray again, aren't the phthalates exposure levels in rodent studies much higher than levels found in mothers and infants, and most research indicate that humans are less sensitive than rodents to phthalates?

Dr. GRAY. Well, on the first question I think that the majority of the literature which is fairly recent and not that large shows that the majority of people and amniotic fluid levels are exposed to very low levels that are well below the doses we use in our animal studies but the distribution of phthalate exposures is several orders of magnitude and there are some very skewed high values resulting from exposure to specific products. We are not always sure what they are. So in those cases we have compared the levels in rats to the levels in humans. They are not as large as we generally would care for, and so when we compare human amniotic fluid levels to rat amniotic fluid levels in affected rats for di-butyl phthalates and metabolite the highest level in humans was only one-fifth that of a dose that produced an effect in the rat. So that is not such a wide margin exposure.

Ms. HOOLEY. Right. But there was also in the Journal of Human Reproduction, one of the things they said is that it was found—humans were found to be 10 times more sensitive than rodents. Do you agree with that statement?

Dr. GRAY. I agree that it must have been published there, but I think that is an—that would have to be considered an interesting hypothesis, and I don't know how you would confirm that.

Ms. HOOLEY. OK. OK. Dr. Bucher, have scientists representing the European Union concluded that DINP is safe?

Dr. BUCHER. I would have to call on Dr. Foster. Do you want to answer that? We are not specifically dealing with issues related to the regulations in the European Union with regard to phthalates.

Ms. HOOLEY. But the European Union did ban six phthalates, right?

Dr. BUCHER. Yes, they did.

Ms. HOOLEY. Pardon?

Dr. BUCHER. Yes, they did.

Ms. HOOLEY. Dr. Bucher, if phthalates are banned, won't the industry be forced to use unsafe alternatives or are there safe alternatives?

Dr. BUCHER. Well, that is an excellent question that any of the panelists might be able to weigh in on. I have no specific information on the substitutes for the phthalates that would be used in place of the banned materials. It is conceivable that they are safe. It is conceivable that they are not safe. Unless we have information on what those are and what kind of testing has been done, it is impossible to tell.

Ms. HOOLEY. My understanding is that there are several big stores like Wal-Mart and Target and Babies-R-Us that said we would promise to remove or severely restrict children's products containing phthalates by the end of this year. Why are they doing that?

Dr. BUCHER. I really can't answer the question. I was under the impression that that was referring to the BPA-containing materials, but I may be mistaken.

Ms. HOOLEY. For any one of you, in 1998 the CPSC released the results of a study on DINP saying that few if any children are at risk from the chemical because the amount that they would ingest does not reach a level that would be harmful. However, the study identified several areas of uncertainty where additional scientific research is needed and the agency asked industry to voluntarily remove phthalates from teethers and rattles. Unfortunately, not all manufacturers have removed phthalates from these products and teethers and other children's products with phthalates have been found on store shelves. Also, the CPSC Chronic Hazard Advisory Panel found that children up to 18 months old who put PVC plastic toys in their mouth may exceed the recommended acceptable intake of DINP. This implies that there may be DINP risk for any young children who routinely mouth plasticized toys for 75 minutes a day or more. Dr. Bucher, shouldn't the CPSC establish federal regulations for phthalates and shouldn't these regulations pre-empt state law?

Dr. BABICH. Well, may I try to answer that question? First of all, you mentioned the 1998 CPSC report where we identify sources of uncertainty, and we recommended three steps to address those sources of uncertainty, a better method to measure migration, a better observational study, and to convene the CHAP, the Chronic Hazard Advisory Panel. We did all of those things. In 2002 we completed our final report which was released towards the end of 2002. Because a separate study gathering exposure data was just beginning while the CHAP was holding their meetings and conferring,

they didn't have the advantage of these data. They had in fact a difficult task trying to estimate what the exposure might be.

Once we had the data to do that accurately, we found that the exposure was extremely low on the order of one microgram per kilogram per day, whereas the acceptable daily intake was 120 micrograms per kilogram per day. And we also found that the mouthing times were quite low on the order of 1 or 2 minutes per day. Even when you look at the upper bounds, 95th, 99th percentiles, the mouthing times were very low, so as a result the exposures were much lower than the CHAP could have anticipated.

Ms. HOOLEY. Just one quick question at the end, and I know my time is up. Dr. Babich, the study that you did, my question is knowing that there are various types of phthalates in toys and studies have shown that combining phthalates together with pesticides have a cumulative effect, would you say your study is representative of real world exposure?

Dr. BABICH. OK. First of all, teethers and rattles have no phthalates.

Ms. HOOLEY. Right.

Dr. BABICH. Some soft plastic toys have phthalates, but primarily DINP. DINP is not like some of the other active phthalates that Dr. Gray spoke about. DINP has some of those same effects but it is much weaker than the other phthalates. So as a result, those endocrine effects, the reproductive developmental effects become less important, and there were other health end points that for DINP were more important. So in that regard it is difficult to say, I think, in the toys we looked at, it is really only DINP that we were concerned about that we looked at. And it is not like some of the other phthalates that we have heard about today.

Ms. HOOLEY. Thank you. Thank you, Madam Chair.

Ms. SCHAKOWSKY. Mr. Stearns.

Mr. STEARNS. Thank you, Madam Chair. Dr. Gray, I have a report here that is from June 10, 2008. There was testimony by Dr. Norris Alderson, Department of Health and Human Services, and in the report he says that the agency, FDA, has been studying BPA for many years and did a final assessment of the chemical in early 2007. And reading from the report, it says FDA's reassessment of possible low dose effects of BPA concluded that the current level of exposure to adults and infants is safe as defined in, and then it mentions the regulation. Yet at the same time the press is carrying reports there are hundreds of studies supporting harm caused by BPA. So based upon this and these other reports, which is it? Well, OK, I can ask Dr. Alderson.

Dr. ALDERSON. As a result of the current review that NTP has conducted and the process they are going through, FDA has since early 2007 been reassessing all available information on BPA. The task force is currently looking at the total exposure from all FDA products.

Mr. STEARNS. I understand that but what you say here is that the low dose concluded that the current level of exposure to adults is safe, so you stand by that, don't you?

Dr. ALDERSON. We still stand by that today.

Mr. STEARNS. Why are there reports, hundreds of studies reporting that there is harm?

Dr. ALDERSON. Well, in the literature there are a lot of studies which Dr. Bucher and his staff have reviewed in their report that do not meet what we call a regulatory standard in determining safe levels.

Mr. STEARNS. Would it be safe to say that a lot of these studies then do not meet a regulatory standard that you did when you did your report?

Dr. ALDERSON. That is true, but I want to emphasize that when we make an assessment we look at all the available data and information regardless of whether it meets the regulatory standard or not. That is what our scientists do, and we assess all of the information.

Mr. STEARNS. Dr. Gray, does the quality of a study matter if it is dictated directly based upon, for example, who is funding it? Have you found in your experience that sometimes that comes into play where the quality of the study is critical? For example, it might be a university, it might be a private foundation or it might be industry itself looking at it.

Dr. GRAY. I think that is irrelevant and prejudicial.

Mr. STEARNS. If, for example, you are saying a university does it as opposed to a private foundation?

Dr. GRAY. Yes, I think that there are excellent scientists in academia, government, and industry, and when our panel, the expert panel on BPA, reviewed studies we never considered who they worked for or who funded the study. We took each study on an individual basis and considered the quality of the experimental design and statistics, and if it didn't meet minimum standards for experimental design and statistics, we determined that they were inadequate. So there were studies from academic, government, and industry labs that fell into that category, and those are the criteria we use to select studies for our review. We want it only based on high quality studies.

Mr. STEARNS. Dr. Gray, the National Toxicology Program Center for Evaluation of Risks to Human Production expert panel sifted through many studies on BPA and disqualified some of them as part of its final assessment. What were the criteria by which these studies were omitted? Were studies funded by industry as well as from other sources disqualified for these reasons?

Dr. GRAY. Well, the criteria that the expert panel used was—in terms of experimental design, did they have a concurrent control group? Did they properly analyze the data and control for the effects that they should have? If they didn't use appropriate statistics then the conclusions of the study might be invalid in that they would think that there is a low dose effect of bisphenol-A when in fact this is random variation, so you can't interpret that study, and so we didn't include those. But the funding, as I said, the funding source was not considered.

Mr. STEARNS. Dr. Alderson, is there anything you would like to add to that?

Dr. ALDERSON. Well, I think Dr. Gray has summarized how we at FDA view all data. When a product comes to FDA, we ask the sponsor to demonstrate the safety of that product, in this case, a food additive, and also the utility of that product. So the burden is on the sponsor to make their case, and they are expected to

present all the data available on this particular subject, whether it is data they have generated themselves, whether it is data in the literature or from other sources that they may have access to. That is the package of information that FDA receives on basically all the products we regulate, not just food additives and in this case food contact materials, so that is a standard we look at for basically everything we do.

On top of that, our scientists themselves go to the literature and see what they can find on their own. For food contact materials, I must tell you that one out of every four applications that comes to FDA for approval is ultimately withdrawn by the sponsor because the sponsor cannot show that it is safe. The burden is on the sponsor.

Mr. STEARNS. Thank you, Madam Chair.

Ms. SCHAKOWSKY. Thank you. Congresswoman DeGette from Colorado.

Ms. DEGETTE. Thank you very much, Madam Chair. I want to follow up on a couple of questions some of my colleagues asked. First of all, Madam Chair, I would ask unanimous consent to put my opening statement into the record.

Ms. SCHAKOWSKY. Without objection, so ordered.[The prepared statement of Ms. Degette follows:]

STATEMENT OF HON. DIANA DEGETTE

Thank you, Madame Chair, and thank you for holding this hearing on phthalates (pronounced THAL-ates) and bisphenol-A (pronounced bis-FEEN-ol-A) (BPA). Today's discussion will help us take another step forward in improving the health of Americans, and particularly kids, across the country.

We started this journey last year, when I'm sure everyone remembers hearing about toy after toy contaminated with excessive lead. Parents were rightfully scared that toys, seemingly harmless play-things, could actually be deadly.

Parents should take heart, though, because Congress is taking action. The House and Senate passed bipartisan legislation to address this problem of dangerous toys and strengthen the relevant regulatory agency, the Consumer Product Safety Commission (CPSC). I'm pleased to be a member of the Conference Committee working out the differences between the two bills, and we hope to see a bill enacted into law quickly.

Unfortunately, our work is not done. Lead is not the only harmful substance found in consumer products, particularly dangerous to infants and children. Phthalates and BPA pose distinct health risks and ones which the Federal Government needs to address.

Phthalates constitute a variety of compounds and are used in a diverse range of products, from toys to cosmetics. They are most often used in plastics to keep them both sturdy and flexible. They are ubiquitous, so everyone is exposed, including children.

The concern is that some phthalates act as endocrine disruptors, interfering with normal development. For example, in numerous animal studies exposure to some phthalates in the womb has been found to affect the development and function of male reproductive organs. One of the developmental abnormalities found is a risk factor for testicular cancer.

There is also scary evidence from human studies. Some phthalates have been associated with premature female breast development, higher rates of pre-term birth, low male sperm count, and poor male sperm quality. One human study even showed a link between some phthalate metabolites and insulin resistance, a precursor to diabetes.

Its clear that exposure to some phthalates for infants and young children is harmful and detrimental to their development. I'm proud to cosponsor legislation sponsored by Representative Hooley, H.R. 4030, to either ban or better regulate six dangerous phthalates. It mirrors steps taken already by the European Union (EU) and California.

BPA, the other topic for discussion today, is also used in plastics and as part of certain resins. Most relevant here, these plastics and resins appear in things like baby bottles, cans which have food or liquids, and food storage containers.

Is BPA leaching out of these items and into our bodies? The answer is yes. Of the people examined by the Centers for Disease Control (CDC), 92 percent had evidence of BPA in their urine.

Is this exposure harmful? While entities in Europe and Japan have found current expected exposure levels to BPA are safe, Canada recently came to the opposite conclusion. It has banned use in baby bottles and is working to otherwise reduce BPA exposure.

As for domestic agencies, the FDA concluded in November of last year that the current use of BPA was safe. Thanks to the ongoing investigation by the Oversight and Investigations Subcommittee into BPA and its uses, we have learned that it appears the two studies the FDA relied upon were industry-sponsored. That would make the FDA's conclusion suspect. I know the Subcommittee has followed-up with the FDA to understand how it reached its conclusion, and we await the FDA's substantive response.

Most significantly, the National Toxicology Program (NTP) at the National Institutes of Health (NIH) released a draft brief in April on BPA. Based on numerous and up-to-date scientific studies it found "some concern for neural and behavioral effects in fetuses, infants, and children at current human exposures [and] some concern for [BPA] exposure in these populations based on effects in the prostate gland, mammary gland, and an earlier age for puberty in females." While its conclusions are based on animal studies, the NTP writes that "the possibility that [BPA] may alter human development cannot be dismissed."

Its our job in Government to protect the public health by removing from use even potentially dangerous products. The findings of the NTP should be a wake-up call. The possibility that BPA could be having such negative effects on the health of our children means we need to seriously consider taking some kind of action. I expect our witnesses today will help elucidate what actions we should take.

Protecting our kids' health and safety is our most solemn responsibility, and if they are being exposed to dangerous compounds the Federal Government needs to get them out of the marketplace right away. We showed last year with respect to lead that Congress can act quickly, and I'm sure we will show the same alacrity with respect to phthalates and BPA.

Again Madame Chair, thank you, and I yield back the balance of my time.

Ms. DEGETTE. Thank you. The first thing, Dr. Babich, is I was listening to your testimony about how certain types of products for children, products that they suck on a lot like pacifiers and so on, phthalates have voluntarily been removed from those products by the manufacturers, is that correct?

Dr. BABICH. Correct.

Ms. DEGETTE. And when were those products—or when were phthalates removed from those products?

Dr. BABICH. About 1999, early 1999.

Ms. DEGETTE. And upon what information did the manufacturers decide to withdraw the phthalates from those products?

Dr. BABICH. Because in 1998 CPSC staff completed a preliminary report which said we don't think there is a hazard or a risk from DINP but there were significant sources of uncertainty, and that is when they voluntarily withdrew DINP from those products.

Ms. DEGETTE. Now, did the FDA have the authority or does the FDA have the authority today to ban DINP from other children's products?

Dr. BABICH. Well, FDA or CPSC?

Ms. DEGETTE. I am sorry, CPSC.

Dr. BABICH. We have the authority, but there are a number of findings that the Commission has to make before they can ban. We have to show that there is an unreasonable risk. We have to show that there is no voluntary standard that adequately addresses the

risks. We have to also apply the least burdensome regulatory action, in other words, a ban is the most severe regulatory option, and we would have to show that labeling or some type of a standard would not be sufficient to address the hazards.

Ms. DEGETTE. So it would be many steps that——

Dr. BABICH. It would be many steps and——

Ms. DEGETTE. And given the—I am sorry. I have limited time. Given the scientific data that all four of you gentlemen have been talking about, in your opinion would there be sufficient data to have ordered a ban?

Dr. BABICH. No. No way.

Ms. DEGETTE. At that time, and there wouldn't be now in your opinion?

Dr. BABICH. And there wouldn't be now.

Ms. DEGETTE. So here is my question, though, based on some preliminary data. Back in the late 1990s these manufacturers voluntarily took DINP out of certain toys but not other toys. Now, I am a parent, and I can tell you that my children when they were infants sucked on a number of other toys, so why hasn't this substance been removed? I can understand them removing it—is it a risk benefit analysis by industry or what?

Dr. BABICH. First of all, their reasoning—it is probably more than one reason, and concern about their products, but the reasoning for those particular products is that they are intended to go into the child's mouth.

Ms. DEGETTE. Yes, but you would agree with me——

Dr. BABICH. But it is backed up by an observational study. Children's mouthing, when we took a careful look at children's mouthing, we thought we were going to find hours per day. The things children mouth on most is their fingers. Second is pacifiers, and everything after that is relatively minor. Yes, children put literally everything you could imagine in their mouth but for insignificant frequency and duration.

Ms. DEGETTE. Let me follow up on that because I was interested in one of the findings, and I was wondering how the Consumer Hazard Advisory Committee was able to conclude that kids would have to mouth toys with DINP for 75 minutes to have concerns about exposure. How did you come up with that standard?

Dr. BABICH. Well, they worked backwards. They said if you are exposed to this much—this much DINP comes out of the product per minute, and of course we had limited data at that time, but taking that information and knowing what the acceptable dose is, they worked backwards and said you would have to mouth for 75 minutes a day to exceed the acceptable dose.

Ms. DEGETTE. There was an extrapolation of the data. Just one last question, and maybe someone else can answer it if you can't. You had said that even though these phthalates were not found to be dangerous, the European Union banned them. Does anybody know why they banned them if the studies have shown that they are not dangerous?

Dr. BABICH. Well, you know, they have this precautionary principle which came up in those discussions, but really I can't say for certain exactly why.

Ms. DEGETTE. And they have a different regulatory structure. They don't have to go——

Dr. BABICH. It is a different system.

Ms. DEGETTE. Excuse me. They don't have to go through all of the steps that the CPSC would have to go through to ban.

Dr. BABICH. Correct.

Ms. DEGETTE. Thank you.

Ms. SCHAKOWSKY. Thank you. The gentleman from Pennsylvania, Mr. Pitts.

Mr. PITTS. Thank you, Madam Chair. Dr. Babich, in your opinion, should I or anyone else who is bottle feeding a baby throw out our BPA bottles specifically because the BPA in the bottle is poisonous to the child?

Dr. BABICH. Well, of course the infant bottles are not in our jurisdiction. They are under FDA's jurisdiction. However, based on the NTP report I don't have any reason to think that you should stop using them.

Mr. PITTS. Dr. Alderson, do you want to comment?

Dr. ALDERSON. I can't add much to what Dr. Babich just said. That is FDA's current position, that based on the information that we are continuing to review at this time, we do not see a need to change baby bottles and go to plastic. We do recommend you follow the directions of those glass manufacturers though.

Mr. PITTS. Anyone else like to comment? Dr. Gray, you participated in the NTP's expert panel review of BPA science, and the expert panel's findings and recommendations document is distinct from the NTP's draft document. The NTP's draft is also different. Can you please describe the differences and how often does the NTP ignore the recommendations of its expert panels?

Dr. GRAY. Well, I do have in my written testimony, I have a table on page 14 where I tried to compare the end points that we ruled on and our levels of concern and the ones of the NTP brief so this is my interpretation. But of the majority of the areas, we agreed on the levels of concern, and there were three areas where they had elevated the levels of concern where we had minimal or negligible. They elevated it to the level of some for the mammary gland, the prostate gland lesions and the age of puberty in females. I think of several hundred papers that represents a minor disagreement on less than 10 publications, and it is not a major discrepancy. It is not like we said it had negligible concern, and they said it had serious concern.

I also think that my interpretation of the final outcome would be the same is that their final decision was that there was some concern, and there was limited evidence of low dose effects of phthalates, and that is based on four end points. And I think it would have been the same if they hadn't elevated because we had some concern for neural behavioral effects based on limited evidence. So Dr. Bucher can clarify if I am wrong about that. So as to how often they ignore the expert panel, my guess would be that they never ignore the expert panel, but they do have the right to consider new data and re-evaluate the data. And they might even differ in their interpretation with the expert panel.

Mr. PITTS. Dr. Bucher, do you want to speak to that?

Dr. BUCHER. Yes, I would agree that we, in fact, never ignore our experts, and, in fact, in the case of BPA, there is enormous, emerging literature. Over 400 studies have been published since the time the first expert panel report came out in April of last year, until now. So we have taken into consideration new information. We have taken into consideration literature that we gleaned from the public comments that we received in response to the expert panel report concerning clarifications, and in almost all cases we have used the same key studies that were considered of high utility by our expert panel in reaching our conclusions. So I would agree with Dr. Gray that these are rather minor differences actually, in interpretation.

Mr. PITTS. Can you please define what is meant by repeatability of results, and why it is important in scientific studies if one's results cannot be repeated, what does that mean for the findings?

Dr. BUCHER. Well, repeatability of results, there are several different interpretations of that. The legal interpretation is that there is sufficient experimental design that is articulated in the reports that if someone wanted to repeat that study they could, in fact, repeat that study. Many of the studies that we have looked at with regard to BPA have been academic studies done in laboratories according to very precise techniques that they have developed, and they are in fact somewhat difficult to repeat exactly in other laboratories if they don't have access to that same distinct technology. However, when we looked at repeatability of the BPA literature what we looked at was repeatability of general end points that were observed in studies that were designed similarly but not necessarily identically, and in other instances one needs to look at the guideline studies or the traditional safety assessment studies as well. In many cases those studies are large, but they are not repeated so repeatability of literature has a lot of considerations to go along with it with regard to looking at a large body of literature.

Mr. PITTS. Are there any sort of official or widely accepted standards regarding scientific practices for the design and execution of a study specifically for a study on which you base a decision on whether or not to ban a substance. Can you please explain the basic elements? What would be the practical effect if we were to disregard the use of these standards?

Ms. SCHAKOWSKY. This will be the last question because we are over time.

Mr. PITTS. Dr. Gray or either one.

Dr. GRAY. Well, each regulatory agency does have test guidelines that they use for many different types of tests including these which we would call multi-generational tests and they do specify end points, numbers of animals, numbers of litters, and they are usually done under good laboratory practices assuring documentation of the chemicals and the dosing solutions. Those standards are included, I think, in almost all the industry studies that are submitted for risk assessment. The academic laboratories don't use those kind of standards for several reasons, just one because they are quite expensive and resource intensive.

Mr. PITTS. My time is up. Thank you, Madam Chair.

Ms. SCHAKOWSKY. Thank you. Mr. Melancon.

Mr. MELANCON. Thank you, Madam Chair. Dr. Babich, the phthalate that has drawn some attention is DINP and it is manufactured in my district, so I got some concern with it. It is commonly used, heavy in molecular weight and very low migration rate, as I understand it. The Consumer Product Safety Commission denied a petition from the Environmental Defense Fund to ban vinyl toys made with DINP in 2003. Can you share with the committee the process and history on the Commission's decision to deny the petition?

Dr. BABICH. OK. The process is any citizen or group can petition the Commission if they provide sufficient data. It is docketed and the staff begins to work on it, and the Commission has to make a decision as to whether to grant or deny the petition. If the petition is granted, then we would begin a rulemaking process. In this particular case, we did a great deal of work to assess, to review all the literature on the health risks and to seek input from the CHAP and the NTP and other experts. We did experimental work to assess the exposure and presented our results to the Commission. Now this petition wasn't just about phthalates. It was about PVC. There were concerns about other additive chemicals, and that also figured into it, but we did our work. We made our recommendation to the Commission and the staff recommended that there was no need to grant the petition and the Commission agreed and voted unanimously to deny the petition.

Mr. MELANCON. The Consumer Product Safety Commission spent 4 years studying the DINP and concluded that there is not demonstrated health risk from its use in toys. Scientists for the European Union spent 10 years studying DINP, and along with the National Institute of Health have reached similar conclusions about the safety of the DINP. Can you specifically cite government agency's review and approval of any of the potential alternatives to DINP?

Dr. BABICH. Well, we don't have any approval over the products or chemicals prior to marketing. We are just beginning to look at the phthalate substitutes. I don't think any of them is as well studied as the phthalates, and for some of them we found very little or no data relating to toxicity.

Mr. MELANCON. How long have we been using phthalates?

Dr. BABICH. Probably long before I was born. I honestly don't know. They have been around a long time. They probably pre-date the regulatory agencies represented here.

Mr. MELANCON. But to an extreme or to a large amount, when you and I were younger, was it just a minor amount of use or is the——

Dr. BABICH. I honestly don't know. As for example, building materials, you know, vinyl is somewhat replacing aluminum and that sort of thing, so, that may mean increased use of these chemicals. Automobiles have more and more plastics, and they are looking for lighter things, so, the market place is complicated, and I am not qualified to talk about that.

Mr. MELANCON. So they told us to quit using galvanized pipe with lead because of the concern with lead. At least I think it was galvanized pipe or other fixtures, and now we are looking at doing away with PVC, is that where we are going?

Dr. BABICH. Well, you know, that is——

Mr. MELANCON. Getting away from it?

Dr. BABICH. That is EPA's jurisdiction, but my understanding is that most building codes don't allow PVC in the water supplies.

Mr. MELANCON. My time has about run out. Thank you, Madam Chair.

Ms. SCHAKOWSKY. Mr. Terry.

Mr. TERRY. Thank you, Madam Chairman. I have got three young boys, and all of our doctor friends told my wife to breast feed, and as I hear one of the concerns is about estrogenic bleaching. I would like to know approximately, and why don't I give this to Dr. Gray first and if there are other folks up here that would like to add in, but approximately how many estrogenic compounds are there in breast milk?

Dr. GRAY. I am not going to give you a specific number, but I can tell you there are estrogens, natural estrogens from the mother, and many other hormones and growth factors naturally in breast milk and in cow's milk. And I don't know, I think there are some indications that those are beneficial early in birth, and the growth factors in prolactin and things like that may be important in neonatal development. So there are estrogens there. There are quite a few publications that have looked at the levels of estrogens and other hormones in breast milk and in cow's milk, but the levels of estrogen fluctuate with the cycle or in cows whether they are pregnant or not. So I think——

Mr. MELANCON. Are there estrogenic properties or estrogens in, I am sorry, in—I just lost the word, and baby bottles—I am sorry, in the milk that is powdered form that you would put into a bottle. Formula, thank you. My goodness. We are only a few years out from that too. Luckily, I didn't have to get up all night.

Dr. GRAY. I can't personally answer that because I don't know the answer. If anyone else knows that.

Mr. MELANCON. Well, what are the difference between what would occur naturally through breast feeding and would could occur from the bottle?

Dr. GRAY. I think that is an interesting question, and it seems to me that what we would really like to know is sort of a mass balance of all of the estrogens the fetus is exposed to and identify the sources and see how much is any particular environmental estrogen or contributing to that exposure. So is the bisphenol-A leaching from the baby bottle contributing at all to the daily body burden or is it insignificant, and I don't think we have that information but it would be a valuable way to approach the situation. It is noteworthy that in humans unlike rats the estrogen levels are quite high in pregnancy in the mother.

Mr. MELANCON. Interesting. Of the totality of the research that has been done, and there has been a lot of discussion about the methodology and repeatability, none of it is focused on the differences between the estrogen, if any, between natural breast milk and formula and from the plastic of the bottle?

Dr. GRAY. There is a lot of literature and research on breast milk and its obvious benefits, and there is a lot of research on cow's milk, and there are actually quite a few publications citing concerns about long-term consumption of cow's milk throughout life

because of the hormones and things like that which are a data base of uncertain stream.

Mr. MELANCON. Anybody else want to get into this discussion?

Dr. GRAY. There is soy formula. Don't forget soy formula. That has got phyto-estrogens in it.

Mr. MELANCON. You have to put something in the baby bottle.

Dr. GRAY. Yes.

Mr. MELANCON. Thank you.

Ms. SCHAKOWSKY. Let me just say that the record will be open for 30 days. Witnesses are invited, if they wish, to add additional materials and members may submit questions that I hope the witnesses, I expect the witnesses, will be willing to answer. So I want to thank you for your testimony and for your expertise. I appreciate your coming. Our second panel of witnesses. First let me introduce and apologize to Ms. Stanley. The identification says Mr., but it is obvious to everyone, and we do apologize for the mistake, Marian K. Stanley, Senior Director at the American Chemical Council. Ms. Stanley holds an MBA in pharmaceutical chemical studies and a BS in chemistry. She currently manages the Phthalate Esters Panel at the American Chemical Council, and is the panel's legislative coordinator. Dr. Ted Schettler is Science Director at the Science and Environmental Health Network. Dr. Schettler has served on advisory committees of the Environmental Protection Administration and National Academy of Sciences. Dr. Schettler is coauthor of Generations at Risk, Reproductive Health and the Environment, and In Harms Way, Toxic Threats to Child Development. Dr. Calvin Willhite is a toxicologist for the State of California's Department of Toxic Substances Control. He also serves on the National Advisory Committee of the U.S. Environmental Protection Agency for acute exposure guideline levels. And Stephen Lester is Science Director at the Center for Health, Environment and Justice. Mr. Lester directs the Technical Assistance Program at the Center for Health, Environment and Justice, which provides scientific and technical assistance to communities concerned about environmental health issues. His Master's degrees are in Toxicology and Environmental health. And we will begin with Ms. Stanley.

STATEMENT OF MARIAN K. STANLEY, M.B.A., SENIOR DIRECTOR, AMERICAN CHEMISTRY COUNCIL, ARLINGTON, VIRGINIA

Ms. STANLEY. Good morning and thank you, Madam Chairperson, Ranking Member Whitfield, and members of the subcommittee, and thank you for this opportunity to testify. I am pleased to be here. Phthalates and bisphenol-A, or BPA, are not exactly terms that roll off the tongue, although of late they seem to be the focus of more and more American consumers who wonder whether products with these materials are safe. More than five decades of scientific scrutiny by institutions around the world support the continued use of phthalates and BPA in consumer products. Phthalates are vinyl plasticizers. They make shower curtains, floors, raincoats, and other household items soft and flexible. They keep vinyl toys soft and flexible so they don't break into small sharp pieces that can be easily swallowed, and they are used in

non-consumer products like IV tubing and blood bags, helping to save lives.

BPA is used primarily to make clear shatter resistant polycarbonate plastic and epoxy resins. For example, BPA is used to make bicycle and football helmets, eyeglass lenses, and baby bottles and sports water bottles. Epoxy resins are widely used as coatings to protect metals from corrosion. For example, as the coating inside most metal cans epoxy resins protect the safety and integrity of canned foods and beverages. Over the last 18 months, media reports have referred to a handful of studies that attempt to link phthalate and BPA exposure to adverse health effects. We are here today, Madam Chairperson, to provide a more complete picture to help put the public's mind at ease.

Let us first talk about phthalates and the numerous government agency assessments that found their use in consumer products is safe. In a 2001 safety assessment of vinyl toys softened with phthalates, the Consumer Product Safety Commission stated that there is, and I quote, "no demonstrated health risk to children from the phthalate most commonly found in toys, DINP." CPSC added that there is, and I am once again quoting, "no justification for banning the use of the phthalate."

The National Toxicology Program had similar findings regarding DINP. The NTP found minimal concern regarding this phthalate, and the Centers for Disease Control and Prevention has tested thousands of Americans for evidence of exposure to phthalates. The CDC data shows that average human exposure is far below levels set by EPA as protective of human health. So there you have three U.S. government agencies finding that phthalates are being used safely in both consumer and non-consumer products. These findings have been mirrored by international agencies. For example, the European Chemicals Bureau stated that the phthalate used in toys is, and once again I am quoting here, "unlikely to pose a risk even for newborns."

As to why the EU parliament opted to ban phthalates in some children's products despite its own agency's finding of safety, it appears that politics, not science, drove that decision. Turning next to BPA, in the past 2 years comprehensive scientific assessments from the European Union, the U.S. National Toxicology Program, Health Canada, NSF International, and the European Food Safety Authority have all been undertaken, and these assessments support the continued safe use of consumer products containing BPA. Very recently, the FDA said we believe there is a large body of evidence that indicates that FDA-regulated products containing BPA currently on the market are safe, and that exposure to levels of BPA for food contact materials, including for infants and children, are below those that may cause health effects.

Recently, the Canadian government for purely precautionary reasons proposed to ban polycarbonate baby bottles. However, their scientific report concluded that research tells us the general public need not be concerned. In general, most Canadians are exposed to very low levels of bisphenol-A, and it does not pose a significant health risk. In conclusion, I want to state that the American Chemistry Council understands that the public wants to be assured that the products they use are safe and have been evaluated using the

best science. And we agree in the case of phthalates and BPA consumers can confidently rely on rich bodies of safety data and the comprehensive assessments from experts in the U.S. and around the world. Thank you again for this opportunity to address the subcommittee. I am prepared to answer your questions regarding phthalates, and my colleague, Dr. Steve Hentges, who is here, is available to answer your questions regarding BPA. Thank you.

[The prepared statement of Ms. Stanley follows:]

STATEMENT OF
THE AMERICAN CHEMISTRY COUNCIL

Hearing on Safety of Phthalates and Bisphenol-A in Everyday Consumer Products
House Committee on Energy and Commerce
Subcommittee on Commerce, Trade, and Consumer Protection
June 10, 2008

SUMMARY OF ACC'S POSITION

The American Chemistry Council represents the leading business of chemistry. Products supplied by the chemistry sector are essential in manufacturing, agriculture, energy, transportation, technology, communications, health, education, defense, and virtually every aspect of our lives. Basic industrial chemicals are the raw materials for thousands of other products including plastics, water treatment chemicals, detergents, pharmaceuticals and agricultural chemicals. These applications include medicines and medical technologies that save lives, computers that expand our horizons, foods we eat, water we drink, cars we drive, homes in which we live, and clothes we wear.

We understand that recent media attention has created public concern and confusion about some of these chemicals – a family of compounds called phthalate esters, and another compound called bisphenol A. We are pleased to present this testimony to help address some of the confusion.

Bisphenol A is a single compound used primarily to make polycarbonate plastic and epoxy resins. It is also used to make resins used as dental sealants and composites. Only trace levels of residual bisphenol A remain in these materials and in consumer products made from these materials.

Phthalate esters describe a family of compounds used in many applications. The largest use is as an additive to plasticize, or soften, polyvinyl chloride. Before the addition of a plasticizer, polyvinyl chloride (vinyl) is actually a hard plastic.

These materials have been in use for decades. They have been subjected to extensive study worldwide, including by independent researchers as well as government agencies, and scientific review is ongoing. U.S. regulatory agencies charged with regulating these compounds in various applications, after reviewing the large body of scientific data, have reached conclusions supporting their safe use in important applications. The scientific evidence supports the continued use of these important materials.

SCIENTIFIC EVIDENCE SHOWS THE PUBLIC NEED NOT BE CONCERNED ABOUT PRODUCTS CONTAINING PHTHALATES

Phthalates are primarily used to make vinyl soft and flexible. Flexible vinyl products are used in our cars, homes and workplaces and in hospitals to help save lives. These phthalates : diisononyl phthalate (DINP), diisodecyl phthalate (DIDP), di-n-octyl phthalate (DnOP), di-(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), and benzyl butyl phthalate (BBP). For instance, BBP is most commonly used in flooring and insulating sealants. DBP is used in adhesives as a solvent for organic compounds and in cosmetics and personal care products. And DEHP is used in medical devices and other vinyl products.

Numerous government risk assessments have demonstrated that exposure to phthalates in toys and children's products generally pose no significant risk to children. Both the U.S. National Toxicology Program (NTP) and the European Union (EU) have performed risk assessments on phthalates, and have generally found no significant risk to children from exposure to these phthalates.[1] For example,

- For BBP, the NTP assessment found "***minimal concern for adverse developmental effects in fetuses and children***" and the EU assessment, which looked at all sources of exposure to children, including toys, found "***no concern for local exposure to BBP***" and "***no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.***" The EU assessment, to be thorough, considered the "unintentional use" of BBP in toys. Even with such use, the EU found no "***no need for further information or testing or risk reduction measures***" to protect consumers, including children.

- For DBP, the NTP assessment found "***minimal concern***" for fetal developmental effects for pregnant women with typical exposure, and "***some concern***" for male fetal development in women with high exposure, though this conclusion was based on exposure estimates that are significantly higher than actual exposures as measured by the CDC.

The NTP's assessments can be found at: http://cerhr.niehs.nih.gov/reports/index.html; the EU assessments are available at: http://www.phthalates.com/RAs.

- For DEHP, the only concerns noted by the NTP for children were from very high exposures of infants or mothers undergoing intensive medical treatments, and "***some concern***" for children older than one year, based on very high assumed exposures from all sources. The EU assessment also expressed some concern for exposures to children. Again, however, DEHP is not used in the manufacture of children's articles that are intended to be mouthed, and the actual risk from exposure to other products is very low.

The European Chemicals Bureau, which managed the risk assessments performed by the EU member states, provided a draft conclusion of the exhaustive safety reviews of the principal phthalate (DINP) used in toys. It stated it was "unlikely to pose a risk" even for newborns. Regrettably, despite the vote of confidence by the Bureau, the European parliament had already moved forward with banning phthalates from some children's products. It was a decision based on politics, not sound science; a mistake that we hope not to see repeated in the United States.

The most relevant government risk assessment with respect to phthalates in toys is the U.S. Consumer Product Safety Commission (CPSC)'s 2001 safety assessment of vinyl toys softened with phthalates, in particular the phthalate that is by far most commonly used in toys – DINP.[2] This extensive risk assessment found "***no demonstrated health risk***" to children from exposure to DINP from toys and child care articles. The CPSC declined to take action on a petition to ban the use of phthalates in children's toys following its intensive review, which had included evaluation of children's behavior in mouthing toys.

Similarly, the NTP risk assessment of DINP found "***minimal concern***" for adverse effects on human reproduction or fetal development and for developmental effects in children. The EU assessment of DINP concluded that exposure to DINP from toys and baby equipment is "unlikely to pose a risk" for infants and newborns and that such exposure "is not considered of concern."

Besides CPSC and NTP, the U.S. Centers for Disease Control and Prevention (CDC) has also tested thousands of Americans for evidence of exposure to phthalates. The CDC data shows that average human exposure is far below

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[2] The CPSC risk assessment package is available at: http://www.cpsc.gov/library/foia/foia02/brief/briefing.html. This URL links to CPSC briefing packages for Fiscal Year 2002. The first seven links on that page are the complete staff briefing package on PVC/DINP.

levels set by the U.S. Environmental Protection Agency (EPA) as protective of human health and that exposure levels are actually declining. Furthermore, the FDA, which regulates medical devices, has said that phthalate-softened devices have been used for years "without apparent ill effect."

In regards to the media attention around this issue, we have seen a number of major news outlets report that phthalates are "toxic and can cause reproductive problems in humans."

- Senator Dianne Feinstein in a press release issued on March 4th claimed phthalates can "interfere with the natural functioning of the hormone system" and "cause reproductive abnormalities and result in an early onset of puberty" in young children. There is no evidence that any phthalate has ever caused any of these effects in young children.
- A PBS report on March 21st by Senior Correspondent Maria Hinojosa said "phthalates help make … teething rings soft and pliable" and that "scientific evidence suggests that exposure to phthalates… may interfere with the sexual development of boys." First of all, phthalates are not used in the manufacture of these products – that is a myth. Furthermore, as stated above, there is no evidence that any phthalate can interfere with the sexual development of boys.
- An Associated Press story on April 8th stated that phthalates are "widely used in such products as baby bottles and teething rings." Again, false information.
- A Los Angeles Times story on April 27th labeled phthalates as plasticizers that are "often found in personal hygiene products that might alter children's hormones." This is a speculative statement that is not supported by the facts, as indicated above.

These statements are simply not true. Phthalates are not used in the manufacture of teething rings or baby bottles, a misinformation propagated by many of these news reports. Furthermore, to imply that phthalates are somewhat responsible for cancer, hormonal disruption or early puberty in children and for reproductive problems in adults also misinforms the public about the true nature of phthalates. While studies in animals have shown effects, actual studies of humans where volunteers were intentionally exposed or where critically ill infants were

exposed to high levels have FAILED to show any of these effects. What gets referenced over-and-over again are a handful of statistical correlations that have not been recognized as demonstrating real cause and effect.

It is unfortunate that these media reports referred to a handful of studies that attempt to link phthalate exposure to adverse health effects. Many of the studies are biased in their design, test only a small sample size or have uncontrollable variables. Other studies ignore or exaggerate real world human exposure or fail to register species differences. Some of these studies are also based on findings in rodents at extremely high exposure levels. Similar studies in primates at similarly high levels do not show these same effects. There is no evidence that these effects have ever occurred in humans.

In today's world, zero exposure to anything is impossible, and with today's advanced analytical techniques, incredibly tiny amounts can be measured. These levels do not necessarily constitute a health risk.

Some of these studies also rely heavily on statistics to demonstrate a correlation, but they cannot prove cause and effect and are often in immediate conflict with government agencies' findings. A recent example is a study led by Shanna Swan of the University of Rochester[3] which claims that the data collected from 85 infant boys and their mothers supports the hypothesis that prenatal phthalate exposure at environmental levels can adversely affect male reproductive development in humans. However, closer scrutiny reveals a number of significant flaws in the study's methodology:

- No adverse effects were detected in this study. This study provides no evidence that reproductive health or fertility of boys are affected by phthalates.
- Although the abstract reported finding a relationship between exposure and anogential distance, the details indicate no such relationship was found. Only after mathematically manipulating the distance measurement to an index was any relationship projected.
- The measurement of anogenital distance is of no known significance in the practice of medicine and has never been related to any reproductive problem in humans.

[3] The Swan study is available at http://www.shswan.com/articles/uploads/45/Swan_2005_Phthalate_AGD.pdf

- Twenty percent of the infant boys were dropped from the study because reliable measurement could not be obtained.
- Conversion of anogenital distance to anogenital index was done incorrectly. Anogenital distance does change with weight and age but the changes are not linear.
- No correction was made for height or premature births when converting anogenital distance to index.
- The single urine samples collected from 85 pregnant women were neither reliable nor valid since they were not adjusted for variable fluid intake, time of day, or other standard procedures. Nor were they taken at a standard time during gestation.
- The researchers used the wrong statistical model to get their results. They used a model that predicts a rapid decrease in anogenital index at low phthalate levels and smaller decreases at higher levels, a relationship that is biologically implausible.
- The overall conclusion of this study was that the authors felt that more research is needed.

The listed faults of the Swan study have led to negative reviews from NTP's Center for the Evaluation of Risks to Human Reproduction (CERHR) who examined the study and refused to consider its conclusions, stating that the results appeared to be "just noise."

Another study that has generated much media attention was conducted by Sheela Sathyanarayana and others at the University of Washington.[4] This study gives no evidence of adverse health effects from expsosure to low levels of phthalates in consumer products. Rather, the study seeks to explore the sources of infant phthalate exposure through the use of baby care products and suggests that consumers limit the "amount of infant care products used and not to apply lotions or powders unless indicated for a medical reason." While we do believe that there is potential value in the study of metabolized phthalates, we take great exception to any effort to draw unfounded conclusions that suggest human health risks are associated with the mere presence of very low levels of metabolized phthalates in urine. Sathyanarayana's report produces data that are decidedly inconclusive because of these shortcomings:

[4] This study is available at http://pediatrics.aappublications.org/cgi/reprint/121/2/e260

- The value of the study is limited in that it provides no information on the sources or levels of exposure.
- It contains unusually wide ranges of values for the phthalate metabolites listed which demonstrates that the values recorded are wildly variable and are inconclusive.
- The report mixes items such as toys and pacifiers with baby care products such as talcum powder and infant shampoo. It is disturbing that the authors of the study do not appear to know that pacifiers made in the United States are made of latex or silicone and are not made with phthalates.

Due to the many shortcomings of this particular study, we do not believe that it adds value to the existing body of research on phthalate esters and we do not believe that it should provide the basis for any specific recommendations or actions on the part of consumers or manufactures.

EXTENSIVE SCIENTIFIC EVIDNECE SUPPORTS THE SAFETY OF BISPHENOL A IN CONSUMER PRODUCTS

Bisphenol A is a chemical building block used primarily to make polycarbonate plastic and epoxy resins. The safety of products made from these materials is supported by a 50 year safety track record of use and an equally long history of testing.

Polycarbonate is a lightweight, highly shatter-resistant plastic with optical clarity comparable to glass. Epoxy resins have an exceptional combination of toughness, chemical resistance and adhesion. The unique attributes of these materials make them ideal for use in a wide array of products, many of which improve the health and safety of consumers.

The manufacturing processes to make polycarbonate plastic and epoxy resins convert virtually all bisphenol A into the plastic or resin, leaving behind only trace levels of residual bisphenol A, typically less than 50 parts per million (0.005% by weight), in the finished materials. Consumers frequently benefit from products made from these materials, but come into contact with very little bisphenol A from use of these products.

Typical Products Made From Polycarbonate Plastic and Epoxy Resins	
Health Care • Eyeglass lenses • Incubators • Critical components of medical devices (e.g., kidney dialyzers, blood oxygenators, drug infusion units)	**Electronic** • Digital media (CDs and DVDs) • Electronic product housings (e.g., cell phones, computers) • Printed circuit boards laminates
Security • Blast and bullet resistant shielding • Police shields • Protective visors	**Sports Safety** • Bicycle and football helmets • Sunglasses and visors • Skiing and diving goggles
Automotive, Marine, and Aerospace	**Building and Construction**

• Headlamp lenses, mirror housings and bumpers • Instrument panels • Primer coatings • Fiber reinforced composites	• Roof, skylight and greenhouse glazing • Corrosion resistant coatings for steel pipes/fittings, structural steel (e.g., bridges), concrete reinforcement bar • Decorative and industrial flooring
Home Appliances • Components of kitchen appliances (e.g., food processors, refrigerators) • Electrical appliance housings	**Food Containers** • Baby and water bottles • Home food storage containers and tableware • Food/beverage can coatings

In recent years, independent government and scientific bodies worldwide have examined the scientific evidence supporting the safety of bisphenol A. In every case, these assessments support the conclusion that bisphenol A is not a risk to human health at the extremely low levels to which people might be exposed.

Each of these assessments comprehensively examined the potential reproductive and developmental toxicity of bisphenol A. Based on the weight of evidence, these assessments uniformly demonstrate that bisphenol A is not a selective reproductive or developmental toxicant. The most recent evaluations of bisphenol A are briefly summarized below along with their key conclusions regarding reproductive and developmental toxicity.

BISPHENOL A IS DEEMED SAFE FOR USE BY THE U.S. FOOD AND DRUG ADMINISTRATION

FDA regulates the use of bisphenol A in food contact materials, such as polycarbonate used in baby bottles and water bottles, and in epoxy resins used to coat cans containing food products. The U.S. Food and Drug Administration (FDA) said in July 2007 that "FDA is unaware of any specific study in which humans exposed to BPA through any food containers experienced miscarriages, birth defects or cancer. Furthermore, human exposure levels to BPA from its use in food contact materials is in fact many orders of magnitude lower than the levels of BPA that showed no adverse effects in animal studies."

More recently (April 2008), in response to public confusion from media reports about bisphenol A, FDA formed an FDA-wide task force to review current research and new information on bisphenol A for all FDA-regulated products. FDA confirmed that it has been reviewing the emerging literature on bisphenol A on a continuous basis. FDA also confirmed that based on its ongoing review, it believes there is a large body of evidence that indicates that FDA-regulated products containing bisphenol A currently on the market are safe and that exposure levels to bisphenol A from food contact materials, including for infants and children, are below those that may cause health effects.

FDA's position is consistent with two risk assessments for BPA conducted by the European Food Safety Authority (EFSA) Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food and the Japanese National Institute of Advanced Industrial Science and Technology. Each of these documents considered the question of a possible low-dose effect and concluded that no current health risk exists for bisphenol A at the current exposure level.

FDA said in April 2008 that it is NOT recommending that anyone discontinue using products that contain bisphenol A while FDA continues its risk assessment process. See http://www.fda.gov/oc/opacom/hottopics/bpa.html.

FDA'S CONCLUSIONS ON BPA ARE CONSISTENT WITH THOSE OF THE EUROPEAN FOOD SAFETY AUTHORITY

The European Food Safety Authority (EFSA) was established by the European Parliament in 2002 to provide the European Commission, the European Parliament and the European Member States with a sound scientific basis for legislation and policies related to food safety. Included in the scope of EFSA's work are assessments of the safety of food packaging and other materials that contact food.

In January 2007, EFSA released a comprehensive assessment of bisphenol A that was conducted by an expert panel consisting of 21 independent scientific experts from across the European Union.

[1] The assessment, which builds upon and updates an earlier assessment,[2] comprehensively evaluated studies on the toxicity, metabolism and pharmacokinetics, and dietary exposure of bisphenol A.

In general, the findings and conclusions of the EFSA assessment are consistent with those of the more recent CERHR evaluation (see below). The assessment established a Tolerable Daily Intake (TDI) of 50 μg/kg bw/day and concluded that "people's dietary exposure to BPA, including that of infants and children, is estimated to be well below the new TDI."

The TDI was based on the most sensitive no-effect-levels from multi-generation studies conducted in the rat and mouse (see below for more information on these studies). For both studies, the most sensitive no-effect-level was for systemic toxicity (e.g., liver effects) at 5 mg/kg bw/day. The no-effect-levels for reproductive and developmental effects in both studies were at a higher dose (50 mg/kg bw/day) than the dose at which systemic effects occurred. The EFSA panel further concluded that "low-dose effects" of bisphenol A in rodents have not been demonstrated in a robust and reproducible way.

BISPHENOL A HAS BEEN EXTENSIVELY REVIEWED BY THE NTP CENTER FOR THE EVALUATION OF RISKS TO HUMAN REPRODUCTION

The Center for the Evaluation of Risks to Human Reproduction (CERHR) was established by the U.S. National Toxicology Program and the National Institute of Environmental Health Sciences in 1998 to serve as an environmental health resource to the public and to regulatory and health agencies. A primary function of CERHR is to assess the potential for adverse effects on reproduction and development caused by agents to which humans may be exposed. This is accomplished through rigorous evaluations of the scientific literature by independent panels of scientists.

The CERHR evaluation comprehensively reviewed the large scientific database on bisphenol A, including:

- Chemistry, use and human exposure
- General toxicology and biological effects (including metabolism and pharmacokinetics)
- Reproductive toxicity
- Developmental toxicity

To reach its conclusions, the expert panel considered the quality, quantity, and strength of the scientific evidence that exposure to bisphenol A might cause adverse effects on human reproduction and/or development of the fetus or infant. The overall findings of the expert panel evaluation were announced at a public meeting in August 2007, and the final CERHR report was released in November 2007. Subsequently, NTP released a draft "Brief" based on the CERHR report on April 14, 2008.[3]

Based on the weight of scientific evidence, the expert panel found no serious or high level concerns for adverse effects of bisphenol A on human reproduction or development. The draft NTP Brief agreed with these conclusions: "the NTP has negligible concern that the exposure of pregnant women to bisphenol A will result in fetal or neonatal mortality, birth defects or reduced birth weight and growth in their offspring," and "the NTP concurs with the conclusion of the CERHR Expert Panel on Bisphenol A that there is negligible concern that exposure to bisphenol A causes reproductive effects in non-occupationally exposed adults, and minimal concern for workers exposed to higher levels in occupational settings." For several specific potential health effects (regarding neural and behavioural effects, and effects on the prostate gland, acceleration in puberty in females, and the mammary gland), the NTP draft Brief expressed "some concern," but again no serious or high level concerns. Additional research was suggested by the NTP draft Brief, since data is inadequate to reach a firm conclusion.

THE EUROPEAN UNION RISK ASSESSMENT SUPPORTS BISPHENOL A'S CONTINUED SAFE USE

Under the EU Existing Substances Directive, the EU conducted a comprehensive risk assessment of bisphenol A that was published in 2003.[4] An updated risk assessment is in the final stages and is expected to be published in 2008.

The EU risk assessment comprehensively evaluated studies on the toxicity, metabolism and pharmacokinetics, and exposure of bisphenol A. In general, the findings and conclusions of the EU risk assessment are consistent with those of the CERHR evaluation. The 2003 risk assessment established an overall no-effect-level of 50 mg/kg bw/day, which was based on the no-effect-level for reproductive and developmental effects in a multi-generation study conducted in the rat. The no-effect-level from the rat multi-generation study has subsequently been affirmed

by the results of a multi-generation study in the mouse (see below for information on both multi-generation studies). The updated risk assessment, based on the most recent scientific information, retains the overall no-effect-level of 50 mg/kg bw/day, now based on both the rat and mouse studies.

The 2003 EU risk assessment was reviewed by the Scientific Committee for Toxicity, Ecotoxicity, and the Environment (CSTEE), which is an independent scientific advisory committee to the European Commission.[5] The CSTEE agreed with the overall no-effect-level and stated that "a number of high quality studies on the reproductive and developmental effects of bisphenol A are already available and do not support low-dose effects." The CSTEE further stated that "there is no convincing evidence that low doses of bisphenol A have effects on developmental parameters in offspring..."

THE JAPANESE NATIONAL INSTITUTE OF ADVANCED INDUSTRIAL SCIENCE AND TECHNOLOGY'S REVIEW SUPPORTS THE CONTINUED SAFE USE OF BISPHENOL A

The Japanese National Institute of Advanced Industrial Science and Technology (AIST), which is affiliated with the Japanese Ministry of Economy, Trade and Industry is Japan's largest public research organization. A comprehensive human health and environmental risk assessment on bisphenol A, conducted by scientists at AIST's Research Center for Chemical Risk Management, was published in November 2005.[6]

Based on a thorough review of the toxicological profile of bisphenol A combined with estimates of human exposure, AIST concluded that "current exposure levels of BPA will not pose any unacceptable risk to human health."

Along with systemic toxicity, a key toxicological endpoint for the AIST assessment was reproductive toxicity. Similar to the EFSA assessment, the most sensitive no-effect-level was 5 mg/kg bw/day for systemic toxicity in a multi-generation study conducted in the rat. The no-effect-level for reproductive toxicity was 50 mg/kg bw/day, at which systemic effects also occurred. The AIST assessment further concluded that findings from studies claiming reproductive effects at much lower doses were not considered to be robust in comparison to the consistent findings from studies reporting no low-dose effects.

HEALTH CANADA'S RECENT REVIEW IS SUPPORTIVE OF CONTINUED USE OF BISPHENOL A

In April 2008, Health Canada opened a comment period on a proposal to ban polycarbonate baby bottles. This event has been the subject of some confusion in the media, because the reviewing scientists concluded "that bisphenol A exposure to newborns and infants is below levels that may pose a risk." The Canadian government nevertheless proposed moving forward with a ban on polycarbonate baby bottles based on a policy decision that the "gap between exposure and effect is not large enough." Canada also proposed to set limits on BPA in infant formula and to work with industry on alternatives for food packaging.

Canada did not suggest that parents and caregivers stop using polycarbonate bottles while the proposal is being considered. Canada did not suggest that stores stop selling polycarbonate baby bottles while the proposal is being considered. Canada did recommend that parents and caregivers continuing to use polycarbonate baby bottles "do not put boiling water in them."

RECENT, HIGH QUALITY ANIMAL STUDIES HAVE BEEN COMPLETED ON BISPHENOL A

The effects of bisphenol A on fertility and reproductive performance have been investigated in three high quality studies in rats and mice using internationally validated guidelines (two-generation and three-generation studies in the rat, two-generation study in mice) and in a continuous breeding study in mice. Developmental toxicity studies in rats and mice have also been conducted.

- No effect on fertility was seen in the rat two-generation study at the four low-dose levels tested (0.2-200 μg/kg bw/day). In the rat three-generation study, a reduction in litter size was seen only at the top dose of 500 mg/kg bw/day, which also produced clear parental systemic toxicity (significant body weight gain reduction in both sexes and renal tubule degeneration in females). No effects on reproduction or development were seen at the five lower doses tested (1 μg/kg bw/day to 50 mg/kg bw/day) and no parental systemic effects were seen at the four lowest doses (5 mg/kg bw/day and below).
- Consistent with the rat studies, bisphenol A produced parental systemic toxicity in the mouse two-generation study at the two highest doses tested

(50 and 600 mg/kg bw/day), resulting in a NOEL of 5 mg/kg bw/day. The NOEL for reproductive and developmental effects was 50 mg/kg bw/day. No treatment related effects were seen at the four lowest doses tested (3 μg/kg bw/day to 5 mg/kg bw/day).

- In the continuous breeding study in mice, no effects on fertility were seen at 300 mg/kg bw/day. Fertility effects were only observed at doses of approximately 600 mg/kg bw/day and above, at which parental systemic toxicity was present.
- No evidence that bisphenol A is a developmental toxicant was observed in standard developmental studies in rats and mice. In rats, a maternal LOAEL and fetal NOAEL of 160 and 640 mg/kg bw/day, respectively, were identified. In mice, maternal and fetal NOAELs were 250 and 1,000 mg/kg bw/day, respectively.

Individually and collectively, these studies, these studies consistently demonstrate that bisphenol A is not a selective reproductive or developmental toxicant.

In addition, effects claimed to occur at low doses in small-scale unvalidated studies, have not been corroborated in the large-scale multi-generation studies conducted according to internationally validated guidelines. Additional detail on these studies is provided below.

Three-Generation Reproductive Toxicity Study in CD Sprague-Dawley Rats

The study followed the US EPA OPPTS test guideline 837.3800, with additional assessments beyond the guideline requirements, and was conducted under Good Laboratory Practice requirements.[7] Strengths of the study include:

- Oral route of administration, which is most relevant for human exposure
- Wide dietary dose range (6 dose groups ranging from 0.015 to 7500 ppm bisphenol A in the diet, corresponding to intakes of approximately 1μg/kg bw/day to 500 mg/kg bw/day)
- Large group size (30 animals per dose level)
- Multiple endpoints examined, including a thorough histologic evaluation

Parental systemic toxicity (a guideline requirement) was produced at the two highest doses, resulting in a NOAEL of 5 mg/kg bw/day. The NOAEL for reproductive and developmental effects was 50 mg/kg bw/day.

Two-Generation Reproductive Toxicity Study in CD-1 Swiss Mice

The study followed the internationally accepted OECD 416 test guideline, with additional assessments beyond the guideline, and was conducted under Good Laboratory Practice requirements.[8] The study was preceded by a full two-generation reproductive toxicity study on 17β-estradiol, which was then also used as a positive control in the bisphenol A study. Strengths of the study include:

- Oral route of administration, which is most relevant for human exposure
- Wide dietary dose range (6 dose groups ranging from 0.018 to 3500 ppm bisphenol A in the diet, corresponding to intakes of approximately 3μg/kg bw/day to 600 mg/kg bw/day)
- Large group size (28 animals per dose level)
- Multiple endpoints examined, including a thorough histologic evaluation

In addition, maternal and paternal toxicity (a guideline requirement) was produced at the two highest doses, additional F1 male offspring were retained for evaluation concurrent with F1 parental males, a positive control was used to demonstrate that the test system was responsive to a known estrogen, and two negative control groups were used to increase the baseline historical database in mice and to define the intrinsic variability in endpoints of interest.

Consistent with the three-generation study in rats, systemic toxicity was identified at the two highest doses, resulting in a no observed effect level (NOEL) of 5 mg/kg bw/day. The NOEL for reproductive and development effects was 50 mg/kg bw/day. Also consistent with the three-generation rat study, no treatment-related effects were found at doses ranging from 3μg/kg bw/day to 5 mg/kg bw/day and the study did not corroborate effects claimed to occur in this low dose range in small-scale studies.

Two-Generation Reproductive Toxicity Study in CD Sprague-Dawley Rats

In a third comprehensive study, bisphenol A has been tested in a two-generation reproductive toxicity study in CD Sprague-Dawley rats.[9] This study,

which focused on low doses, followed the internationally accepted OECD 416 test guideline and was conducted under Good Laboratory Practice requirements. Strengths of the study include:

- Oral route of administration
- Large group size (25 animals per dose level)
- Wide variety of hormonally sensitive endpoints examined, including behavioral measurements

Consistent with the three-generation rat study and the two-generation mouse study, no treatment-related effects were found in the low-dose range from 0.2 to 200 μg/kg bw/day and the study did not corroborate effects claimed to occur in this low dose range in small-scale studies.

National Toxicology Program Continuous Breeding Study in Mice

Bisphenol A was administered in the diet during a one-week pre-mating period and a 14-week mating trial to groups of twenty male and female CD1 mice (F0 generation) at concentrations of 0, 0.25, 0.5 or 1.0%; daily intakes of bisphenol A are estimated to have been 0, 300, 600 and 1200 mg/kg bw/day in males, and 0, 325, 650 and 1300 mg/kg bw/day in females.[10] In the continuous breeding phase, a statistically significant decrease in maternal body weight was observed after each litter (between 6 and 9%), at the top dose, on postnatal day 0 compared to controls. At study termination, a small but statistically significant decrease in body weight (4%) was observed in treated females compared to controls.

A subsequent one generation study to further evaluate parental toxicity of bisphenol A to CD1 mice observed significant parental toxicity at doses of 650 or 1300 mg/kg bw/day.[11] Key evidence of parental systemic toxicity was increased liver and kidney weights with hepatocellular hypertrophy and renal tubule degeneration/regeneration, reduced body weights and body weight gain. In the continuous breeding study, a statistically significant decrease compared to controls was observed in the number of litters produced per pair (4.5 and 4.7 compared to 5.0 for controls), litter size (6.5 and 9.8 compared to 12.2 for controls) and the number of live pups per litter (6.3 and 9.7 compared to 12.1 for controls) in the high and mid-dose group. No effects on fertility were observed in the low-dose group. A statistically significant decrease in litter size (controls: 11.4, treated males: 9.1, treated females: 5.9) and number of live pups per litter (controls: 11.3,

treated males: 8.4, treated females: 5.5) were observed in the cross-over mating. In the continuous breeding phase, a statistically significant decrease in live pup weight (6%) on postnatal day 0 was observed in females at the top dose after adjustment for litter size, including live and still births. In the continuous breeding phase a small but statistically significant decrease in body weight gain (4%) was only observed in treated females at study termination. No effect was observed on the sex ratio in the F1 generation. In the F1 litters used in the cross-over breeding experiment, post natal (day 0) pup weights were significantly increased in males (9-11%) and in females (8-10%) in the mid- and high-dose.

This study, conducted at high doses, is superseded by the more recent two generation study in mice.

National Toxicology Program Developmental Toxicity Study in Mice

Bisphenol A has been tested for developmental toxicity in a NTP study using CD-1 mice.[12] Two tests were performed and as the same signs of maternal toxicity were observed in both tests the data were combined. Groups of 29-34 time-mated female mice were gavaged with 0, 500, 750, 1000 or 1250 mg/kg bw/day in corn oil on days 6 to 15 of gestation. Animals were sacrificed on day 17 of gestation and the fetuses were subjected to routine external, visceral and skeletal examinations. Data were also provided on the additional dose level of 250 mg/kg bw/day, which was used only in the first test. Some maternal deaths were observed at doses of 750 mg/kg bw/day and above and a decrease in maternal body weight gain of 4-10% and 32-43%, for both the treatment and gestation period was observed at 1,000 and 1,250 mg/kg bw/day, respectively. Other significant signs of maternal toxicity were observed at 500, 750, 1000 or 1250 mg/kg bw/day as well as a dose-related statistically significant increase in mean relative liver weight (9-26%) was observed in dams in all bisphenol A treatment groups as compared to controls. At 1250 mg/kg bw/day a statistically significant increase was observed in % resorptions per litter (40% as compared to 14% in controls). A dose-related decrease in mean fetal body weight per litter was observed in the bisphenol A treated groups that was statistically significant at 1,250 mg/kg bw/day when compared to the control value; 1%, 1%, 9% and 14% at 500, 750, 1,000 and 1,250 mg/kg bw/day, respectively. No statistically significant effect was observed on the number of implantation sites per dam, the number of live fetuses per litter and the sex ratio. Bisphenol A administration had no significant effect on the % of fetuses malformed per litter or the % of litters with malformations. Overall, a significant

increase in resorptions and decrease in fetal body weight was observed only at 1,250 mg/kg bw/day in the presence of severe maternal toxicity.

National Toxicology Program Developmental Toxicity Study in Rats

Bisphenol A was studied for developmental toxicity potential in a NTP study.[13] In the main study, two trials were performed and the data from both tests were combined. In total, groups of 27-29 time-mated CD rats were gavaged with 0, 160, 320, 640 or 1,280 mg/kg bisphenol A in corn oil on days 6 to 15 of gestation. Animals were sacrificed on day 20 of gestation and the fetuses were subjected to routine external, visceral and skeletal examination. At 1,280 mg/kg, deaths were observed in 7/27 females and because of this high mortality rate, the top dose group was not included in statistical analyses. Compared to controls, a statistically significant decrease in mean maternal body weight gain was observed in dams at all dose levels for the treatment period (35-54%) and the gestation period (11-14%). No effect was observed on gravid uterine weights. When maternal body weight gain was corrected for gravid uterine weight a statistically significant decrease was still apparent at all dose levels (26-34%). Pregnancy rates were not affected by treatment with bisphenol A, nor was there any effect on the number of implantation sites per litter, % resorptions per litter, number of live fetuses per litter, sex ratio, mean fetal body weight per litter, % fetuses malformed per litter and % litters with malformed fetuses. In conclusion, this study provides no evidence of developmental toxicity in the rat at exposure levels which are toxic to the mother. A maternal NOEL could not be identified; instead a LOAEL of 160 mg/kg was identified for clinical signs of toxicity and a statistically significant decrease (26%) in body weight gain. No fetal effects were seen at the highest dose level evaluated, 640 mg/kg.

"LOW-DOSE" STUDIES ARE UNVALIDATED

Although bisphenol A has been shown to have some weak "estrogen-like" activity in a number of in vitro and in vivo screening assays, molecular biology studies[14] have demonstrated that bisphenol A does not act as a weak estrogen mimic but exhibits a distinct mechanism of action from estradiol at the estrogen receptor. Nevertheless, the potency of this activity in screening assays generally ranges from 3 to 5 orders of magnitude less than that of estradiol.

It should also be noted that many of the studies investigating endocrine modulating activity are essentially screening tests and many employ experimental protocols that have not been validated. This information in conjunction with the known extensive metabolism of bisphenol A to non-estrogenic metabolites (see below) provides a scientific basis for the lack of toxicological effects at low doses in the multi-generation studies described above. Effects claimed to occur at low doses in small-scale unvalidated studies have not been corroborated in the large-scale multi-generation studies conducted according to internationally validated guidelines.

The small-scale unvalidated studies have been evaluated in the comprehensive assessments described above. Each of these assessments applied a "weight-of-evidence" approach to evaluate the body of information available for bisphenol A. Each assessment relied on the results of the two- and three-generation studies described above for its overall conclusion.

METABOLISM AND PHARMACOKINETICS DATA SUPPORTS RESULTS FROM ANIMAL STUDIES

The potential for a substance to cause reproductive or developmental toxicity is substantially influenced by metabolism and pharmacokinetics. These parameters have been very well characterized for bisphenol A in numerous animal studies (i.e., rodents and primates) and in several human volunteer studies.

Overall, these studies indicate that bisphenol A has a low potential to cause adverse health effects in humans and, in particular, effects mediated by an estrogenic mode of action. Key findings from these studies are summarized below:

- **Humans Efficiently Metabolize and Eliminate Bisphenol A from the Body**
  Human volunteer studies confirm that bisphenol A is efficiently metabolized to a glucuronide conjugate after oral exposure.[15,16,17] Studies in animals and with isolated liver cells have shown that this metabolic process occurs in the intestinal wall[18] and in the liver,[19,20,21,22] both of which must be crossed before bisphenol A can enter into circulation in the body after oral exposure.

  In the first human study, volunteers were treated with a single 5 mg oral dose of bisphenol A per person, which is approximately 1000 times greater

than a typical daily intake of bisphenol A (see Section 6 below). No parent bisphenol A was found in blood at any time point and all bisphenol A was excreted in urine as the glucuronide. The elimination half-life for the glucuronide conjugate was approximately 4 hours, which means that any bisphenol A to which people are exposed should virtually all be eliminated from the body within approximately 24 hours.

- **Bisphenol A Has Low Bioavailability and Does Not Accumulate in the Body**
  The human volunteer studies confirm that bisphenol A has very low bioavailability (i.e., very little parent bisphenol A will reach target tissues) after oral exposure. The rapid elimination of bisphenol A indicates that bisphenol A has very low potential (if any) to bioaccumulate in the body.

  Low bioavailability, efficient metabolism of bisphenol to the glucuronide, and low potential to bioaccumulate have also been demonstrated in numerous studies on laboratory animals, some of which are cited here.[23,24,25,26,27,28,29] Included are studies that demonstrate that metabolism of bisphenol A is not altered during pregnancy[30] and that neonatal animals also efficiently metabolize bisphenol A from an early age in neonatal life.[31]

- **Bisphenol A Metabolites are Not Estrogenic**
  The primary metabolite of bisphenol A, the glucuronide, has been shown to exhibit no estrogenic activity.[32] The bisphenol A sulfate metabolite, which may be present at lower levels, has also been shown to exhibit no estrogenic activity.[33] These studies indicate that bisphenol A is not likely to cause estrogenic effects since the metabolites of bisphenol A that enter the body have no known biological activity and, in particular, have no estrogenic activity.

BISPHENOL A PRESENTS VERY LOW POTENTIAL FOR HUMAN EXPOSURE

Numerous studies have been conducted to directly measure human exposure to bisphenol A by urinary biomonitoring and to indirectly estimate human exposure by analysis of potential sources of exposure. These data consistently indicate that human exposure to bisphenol A is essentially all through the diet and is extremely low. Typical human exposure to bisphenol A is less than 0.1 μg/kg bw/day. Key findings from these studies are summarized below:

- **Biomonitoring Studies Confirm Extremely Low Human Exposure**
  Since the glucuronide metabolite of bisphenol A is rapidly and completely eliminated into human urine, human exposure can readily be estimated by urinary biomonitoring for bisphenol A (after hydrolysis of conjugates). Numerous studies conducted worldwide indicate that typical human exposure to bisphenol A is less than 0.1 μg/kg bw/day.

  The largest study was conducted by the US Centers for Disease Control and Prevention as part of their NHANES 2003-2004 program.[34] This study reported urinary bisphenol A data for more than 2500 individuals ranging in age from 6-85. Due to the study design, the data is representative of the US population. In this study, the median concentration of bisphenol A in urine (after hydrolysis) was 2.8 ng/ml. Based on this data, the typical daily intake of bisphenol A for the population is estimated to be approximately 0.05 μg/kg bw/day.

  Many smaller-scale studies from Japan[35,36,37,38,39], Korea,[40,41] Europe,[42] and the US[43,44,45,46,47,48,49] have reported similar results. Included are two studies in which urine samples were collected over 24-hour periods.[50,51]

- **Potential Exposure From Consumer Products is Very Low**
  Consumer products made from polycarbonate plastic or epoxy resins contain only trace levels of bisphenol A, typically less than 50 parts per million (0.005% by weight), which limits potential exposure to bisphenol A from use of products. Human exposure to bisphenol A is essentially all through the diet[52] and numerous studies have been conducted to examine the potential for bisphenol A to migrate from polycarbonate plastic or epoxy resins into a food or beverage. Of particular interest are the many studies on polycarbonate baby bottles[53,54,55,56,57,58] and canned foods and beverages.[59]

  Calculated human exposure estimates based on measured migration data combined with consumption patterns[60] are generally consistent with exposure estimates directly measured by biomonitoring. Both confirm that human exposure to bisphenol A from all sources, including from use of consumer products, is extremely low.

- **Exposure to Bisphenol A Is Within Government-Set Safe Limits**
  The European Food Safety Authority recently established a Tolerable Daily Intake for bisphenol A of 50 µg/kg bw/day based on an up-to-date scientific review. This value is identical to the Reference Dose set by the US Environmental Protection Agency.[61] The typical daily intake of bisphenol A is approximately 1,000 times lower than these acceptable levels and poses no known risks to human health.

CONCLUSION

From a toxicological perspective, BPA and phthalates are among the most well defined chemicals on earth. They have been the subject of hundreds of studies in lab animals and numerous government-sponsored assessments. Accordingly, based on the science and the use patterns for these compounds, no restriction on their uses in current applications is warranted at this time.

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[3] Information on the CERHR evaluation, including the April 14 NTP draft brief, is available at http://cerhr.niehs.nih.gov/chemicals/bisphenol/bisphenol.html. The final report will also be posted on this site.

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Ms. SCHAKOWSKY. Thank you. Dr. Schettler.

STATEMENT OF TED SCHETTLER, M.D., M.P.H., SCIENCE DIRECTOR, SCIENCE AND ENVIRONMENTAL HEALTH NETWORK, ANN ARBOR, MICHIGAN

Dr. SCHETTLER. Thank you, Madam Chair, members of the committee. Thank you for the opportunity to comment today on the safety of phthalates and bisphenol-A. My name is Ted Schettler. I am a physician. I have both a medical degree and a Master's in public health with training in toxicology and epidemiology, as well as the traditional medical sciences. I participated in an investigation of phthalate exposures in infants in two hospitals. I have published papers and monographs addressing phthalate exposures and toxicity. I am currently the Science Director of the Science and Environmental Health Network. I have provided you with some written comments, and I will briefly summarize those now.

The chemicals that we are discussing today are in the bodies of virtually every American. They are in fetuses, infants, and children. Health impacts linked to these chemicals are determined from animal testing and to a limited extent in humans, are among those that are prominent in people today, so today's topics are of obvious public health concern. First I will comment on phthalates. People in the general public are regularly exposed to mixtures of phthalates because of their widespread use in consumer products and general environmental contamination. Some individuals are exposed at much higher levels than others. Phthalates cross the placenta and the developing fetus is also exposed. Members of the phthalate family of chemicals have both similarities and differences in their chemical structures. Some phthalates have enough in common to cause similar toxic effects.

This means that when we estimate risks, we need to consider phthalate exposures in the aggregate, not simply risks associated with single chemicals from single sources. The developing male reproductive tract is particularly vulnerable to phthalates. Exposures in laboratory animals, as we have heard, cause a variety of malformations, including hypospadias, which is a birth defect of the penis with increasing incidence in baby boys in birth defect registries in the United States, undescended testes, and reduced sperm counts. At least six different phthalates interfere with normal testosterone production. That helps to explain how they alter reproductive tract development. When they are studied in mixtures, their doses are additive.

This is a critical issue for public health protection. People are not exposed to single phthalates, but rather to mixtures. We need to think about that when drawing conclusions about risk. Some people are exposed to single phthalates at particularly high levels. In our study in two Boston hospitals, for example, we determined that some infants were exposed to DEHP from medical devices at levels in excess of FDA's tolerable intake. When exposures are considered in the aggregate, as they should be for a subset of these chemicals, the number of people with excessive exposure is much larger. Studies of phthalates in humans are limited although evidence consistent with impacts at current exposure levels is beginning to accumulate.

For example, a study of baby boys found a correlation between maternal exposures to four different phthalates and altered genital development. We don't know what the implications of these findings are for future health of reproductive success of these boys but in laboratory animals a shortened ano-genital distance, which is what is seen in these children, is often predictive of compromised reproductive success in adulthood. Phthalates are also linked to reduced sperm count or sperm quality in men studied and in infertility clinics. A study in Denmark found altered sex hormone ratios in boys whose mothers had higher levels of some phthalates in their breast milk. There are other health effects that haven't been mentioned today linked to phthalates in building materials and household furnishings, including asthma, other respiratory illnesses, and allergies.

Let me conclude with a few comments about bisphenol-A. There are different divergent opinions about health risks associated with this chemical, and I want to make several points. First, studies from the CDC undeniably show that exposure to bisphenol-A is widespread in the general population. Second, in addition to the biologically inactive metabolite of bisphenol-A, the active form is also regularly detectable in the blood of people. Third, fetuses and infants have markedly reduced capacity to transform the active form of bisphenol-A into the inactive form that is excreted in the urine, and for that reason fetuses and infants are at particular risk of prolonged exposure.

Fourth, based on a large scientific data base, the committees that we have heard about earlier today have enumerated a number of health risks, but I want to focus on just a couple of them to finish up here. We have heard about the neural behavioral changes, which, by the way, do not just occur by injecting the chemical into the brain, but happen in animal studies where the animals were exposed orally at levels that are approximately equivalent to what humans are exposed to, and we have heard about others as well. But animal testing shows that low level bisphenol-A during fetal development modifies the development of the prostate gland and breast, permanently altering their disease architecture. Moreover, these architectural changes predispose the prostate and breast to later disease, including cancer.

In some cases, these changes are themselves pre-cancerous. From a public health perspective, this is a serious concern. If these same tissue alterations occur in people, and the presumption ought to be that they do unless it is shown otherwise, we are faced with a troubling reality. That means that virtually all fetuses and infants in the United States are exposed to a chemical at levels that may increase the risk of prostate or breast cancer years later. Today's patterns of disease and disabilities prominently include prostate and breast cancer, diabetes, early onset of puberty in girls, behavioral abnormalities in children, infertility, and birth defects of the reproductive tract, including hypospadias.

Each of these conditions has been linked in some way from the literature that you have heard about today to phthalates or bisphenol-A. Whereas, there are many different interpretations of some portion of the scientific database, it is undeniable that all Americans are exposed to these chemicals. So I urge you to think

about this from a public health perspective and ask what amount or strength of evidence we should require before taking action to reduce or eliminate exposures, particularly in vulnerable populations. This is a public policy decision which should be informed by good science, but also by values and common sense. Do we need to wait for irrefutable proof of harm? The limits of epidemiologic research will always make it difficult to tease out some cause and effect relationships even when they exist. It is particularly difficult when the entire population is exposed to the chemicals of concern.

Policymakers need to decide when evidence is sufficient to act even in the face of uncertainty; otherwise, we miss important opportunities for the primary prevention of disease and disability. Thank you very much for the opportunity to comment today.

[The prepared statement of Dr. Schettler follows:]

Subcommittee on Commerce, Trade, and Consumer Protection

Testimony of Ted Schettler MD, MPH

Science Director

Science and Environmental Health Network

June 10, 2008

Thank you for the opportunity to comment today on the safety of phthalates and bisphenol A in consumer products. My name is Ted Schettler. I am a physician. I received a medical degree from Case Western Reserve University and master's degree in public health from Harvard University. I have training in toxicology and epidemiology in addition to traditional medical sciences. I practiced medicine for over 30 years.

I have participated in an investigation of phthalate exposures in infants in intensive care units in two hospitals. I have published papers and monographs addressing phthalate exposures and toxicity. I am currently the Science Director of the Science and Environmental Health Network with an office in Ann Arbor, MI. This Network engages communities and governments in the effective application of science to protect and restore public and ecosystem health.

The chemicals being discussed today are in the bodies of virtually every American. They are in fetuses, infants, and children. Moreover, health impacts of these chemicals, as determined from animal testing and to a limited extent in humans, are among those that

are prominent in today's patterns of disease. Therefore, today's topics are of obvious public health concern.

First, I will comment on phthalates:

Phthalates are produced in large amounts and used in many consumer products, including, toys, construction materials, furnishings, appliances, medical devices, pharmaceuticals, insect repellants, pesticide formulations, adhesives, paints, inks, cosmetics, personal care products, air fresheners, and others. In general, phthalates are not tightly bound in these products, and people are exposed when they use them or from general environmental contamination.

Biomonitoring data from the Centers for Disease Control and Prevention (CDC), as well as a large number of epidemiologic studies, show that people in the general public are regularly and consistently exposed to mixtures of phthalates. This includes all age groups, including developing fetuses and infants. Some people are exposed at much higher levels than others.

Members of the phthalate family of chemicals have both similarities and differences in their chemical structures. As a result, their toxic properties vary to some degree. Nevertheless, some phthalates have enough in common to cause toxic effects in laboratory animals and people through the same mode of action. This means that when

we estimate risks associated with phthalates, we need to consider exposures in the aggregate—not simply risks associated with single chemicals from single sources.

Animal testing shows that the developing fetus and infant are particularly sensitive to phthalates. Effects on the developing male reproductive tract have received considerable attention. Exposures to some phthalates in laboratory animals at critical times during the formation of the reproductive tract cause a variety of malformations, including hypospadias (a birth defect of the penis with increasing incidence in baby boys in birth defect registries in the US) , undescended testes, and reduced sperm counts.

Studies designed to elucidate how phthalates cause these abnormalities show that at least six members of the family, and possibly more, interfere with normal testosterone production. (DEHP, DBP, BBzP, DINP, DiBP, DPP) (Borch, 2004; Howdeshell, 2008) To some extent, the potency of these six phthalates varies with respect to their ability to interfere with testosterone production. But when studied in mixtures, their doses are additive.

This is a critical issue for public health protection. People are not exposed to single phthalates but rather to mixtures of these chemicals in the real world. It is essential to consider these exposures collectively when drawing conclusions about the risks associated with exposures to any particular phthalate or from any particular source.

Some people are exposed to single phthalates at levels that exceed safety thresholds as determined by regulatory agencies. In our study in two Boston hospitals, for example, we determined that some infants were exposed to DEHP from medical devices at levels in excess of FDA's tolerable intake. When exposures are considered in the aggregate, as they should be for a subset of these chemicals, the number of people with excessive exposures is much larger.

Reproductive toxicologists generally agree that the effects of phthalates in rodents and other test animals are relevant to people. Studies in humans are limited, although evidence of phthalate impacts in people at current exposure levels is beginning to accumulate. For example, a study of 134 baby boys found a correlation between maternal exposures to four different phthalates and altered genital development in their sons. (Swan, 2005) Phthalates are also linked to reduce sperm count or sperm quality in men studied in an infertility clinic. (Hauser, 2006)

Some phthalates do not interfere with testosterone production but nevertheless have toxic properties. DIDP, for example, causes birth defects and decreased survival and growth of offspring in laboratory animal testing. DIDP has historically been used in toys. (NTP-CERHR monograph)

Other health effects in people that have been linked to phthalates in building materials and household furnishings include asthma, other respiratory illnesses, and allergies.

(reviewed in Mendell, 2007) Animal studies also show that DEHP can boost the allergic response to other substances, often at very low levels of exposure.

I will conclude with a few comments about bisphenol A.

First, studies from the CDC show that exposure to bisphenol A is widespread in the general population. Ninety-three percent of people in the representative study population had detectable levels of bisphenol A in their urine. Levels were higher in children than adults. People are exposed to bisphenol A primarily through their diet. Bisphenol A can migrate into food and beverages from the lining of food cans or from polycarbonate plastic containers made from bisphenol A. Skin absorption and inhalation may be also be significant exposure pathways that are not well quantified.

Second, in addition to the biologically inactive metabolite of bisphenol A, the active form of the chemical bisphenol A is also regularly detectable in people. The active form is also present in umbilical cord blood of newborn infants showing unequivocally that fetuses are exposed to that form of bisphenol A in the womb. (Schonfelder; reviewed in Vandenberg; NTP-CERHR)

Third, fetuses and infants have markedly reduced capacity to transform the active form of bisphenol A into the inactive form that is excreted in the urine. (NTP-CERHR; Taylor, 2008) This means that fetuses and infants are at particular risk of prolonged exposure to the active form of bisphenol A.

Fourth, bisphenol A has estrogen-like properties and can also disrupt thyroid hormone status. Based on a large scientific database, committees convened by the National Toxicology Program, the National Institute of Environmental Health Sciences, and other experts have enumerated a number of health concerns associated with bisphenol A, although lack of consensus about how to interpret the data as a whole persists. Health effects that have been described include neurobehavioral changes, impacts on reproductive system development and function, abnormal numbers of chromosomes in dividing cells, predisposition to cancer, and insulin resistance as is seen in diabetes. In laboratory animal tests, some of these effects occur with low-level exposures, similar to those in people in the general population. I want to comment from a medical and public health perspective on just two of these.

Animal testing shows that low-level bisphenol A exposures during fetal development or infancy modify the development of the prostate gland and breast, permanently altering their tissue architecture. (Prins, 2008; Timms, 2005; Durando, 2007) Moreover, these architectural changes predispose the prostate and breast tissue to later disease, including cancer. In some cases, these changes are themselves pre-cancerous. These abnormalities occur in animal studies at levels of exposure similar to those to which people in the general public are now exposed.

From a public health perspective, this is a serious concern. If the same tissue alterations occur in people, and the presumption should be that they do unless shown otherwise, we

are faced with a troubling reality. Virtually all fetuses and infants in the US are exposed to a chemical at levels that may increase the risk of prostate or breast cancer years later.

Today's pattern of diseases and disabilities prominently includes prostate and breast cancer, diabetes, early onset of puberty in girls, behavioral abnormalities in children, infertility, and birth defects of the reproductive tract, including hypospadias. Scientific studies, designed in various ways, have linked each of these conditions to phthalate or bisphenol A exposures, although there are differing interpretations of some portions of the scientific database. It is, however, undeniable that virtually all Americans are exposed to phthalates and bisphenol A.

I urge you to think about this from a public health perspective and ask what amount or strength of evidence we should require before taking action to reduce or eliminate exposures to these chemicals, particularly in vulnerable populations. That is a public policy decision, which should be informed by good science, and also by values and common sense. Do we wait for irrefutable proof of harm in people before taking action? Who decides?

The limits of epidemiological research will always make it difficult to tease out some cause and effect relationships, even when they exist. It is particularly difficult when the entire population is already exposed to chemicals of concern. But policy makers need to decide when evidence is sufficient to act, even in the face of scientific uncertainty.

Otherwise, we miss opportunities for primary prevention of avoidable disease and disability.

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Ms. SCHAKOWSKY. Dr. Willhite.

STATEMENT OF CALVIN WILLHITE, PH.D., STATE OF CALIFORNIA, DEPARTMENT OF TOXIC SUBSTANCES CONTROL, BERKELEY, CALIFORNIA

Mr. WILLHITE. Good morning, Madam Chairman and committee members.

My name is Calvin Willhite, and I am a toxicologist with the State of California. However, none of my written or verbal testimony should be interpreted as representing that of the State of California. I am here today on behalf of NSF International, which used to be called the National Sanitation Foundation, and their health advisory board. Today I am going to speak about bisphenol-A, a chemical that some people consider dangerous, but first I would like to start with a short story.

All parents tell their children that there are no such things as ghosts, but one night at Boy Scout camp the Scoutmaster told us a story about something that was in the Okefenokee swamp, and we 10-year-old children believed that.

Developmental toxicology has many ghosts and many villains. An example of a ghost is Bendectin, a drug used for more than 30 years to control nausea and vomiting in pregnant women. Sensational press reports and over 300 lawsuits alleged that it caused birth defects. Subsequent studies proved that was absolutely false. An example of a villain is the Japanese Nitrogenous Fertilizer Company, who discharged mercury into Minamata Bay and poisoned at least 800 people, caused fetal encephalopathy, and killed at least 100.

So is bisphenol-A a ghost or is it a villain? Bisphenol-A is the substance used to make polycarbonate plastic and epoxy resins. From this plastic we have all sorts of products, including beverage containers and bicycle helmets. The resins are used to line food cans.

Is bisphenol-A dangerous? All scientists agree that bisphenol-A has estrogen-like activity. They just disagree about how powerful it is. Some contend it causes toxicity at very low doses. Others find it causes no such effects even at high doses. These differences are mainly due to how the chemical is given to lab animals; that is, whether it is injected or given by mouth. Since nearly all human exposure comes from food, and since all regulatory agencies agree that if humans are exposed to a chemical by food, the compounds should be given orally. In our work at NSF, we used the laboratory studies that gave bisphenol-A orally to derive a safe upper limit of exposure for bisphenol-A in drinking water. Therefore, what we now need are safe limits to control the levels of bisphenol-A in infant formula, food, and beverages. We already have the National Academy of Sciences methods for establishing those limits. So to discuss the danger of chemicals like bisphenol-A, we should use those methods.

People have their own opinions about how dangerous bisphenol-A might or might not be but a personal opinion doesn't matter. To answer the question whether bisphenol-A is harmful or not, we need evidence-based toxicology to define what is called the margin of exposure. For example, the World Health Organization has al-

ready established a safe, upper limit of exposure for another endocrine disrupter. That chemical is named zearalenone. It is present in pastries, infant food, and even beer because zearalenone is produced by a fungus that grows on barley, corn, wheat, and rice. Zearalenone is hyperestrogenic. It is one-tenth as powerful as the natural estrogen in our body. By comparison, bisphenol-A is one fifteen-thousandths as powerful.

How can we implement a ban on zearalenone? Does that mean a ban on donuts and beer? The answer is we couldn't. Only after we define safe limits can we gauge the relative hazard or safety of exposure to zearalenone, bisphenol-A, or any other chemical. And by the way, a famous American once wrote: "There is something fascinating about science. One gets such wholesale returns of conjecture out of such trifling investments of fact." That famous American was Samuel Longhorne Clemens. Thank you.

[The prepared statement of Dr. Willhite follows:]

BISPHENOL A AND PUBLIC HEALTH

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WHAT IS BISPHENOL A?

Bisphenol A (called BPA for short) is a small molecule used to build polycarbonate plastics and to formulate epoxy resins. Polycarbonate plastics are used in manufacture of bicycle safety helmets, athletic shin guards and plastic beverage containers. The epoxy resins are used to line metal containers that store food and beverages. Because bisphenol A has some estrogen-like pharmacologic activity, it is one of a class of substances commonly known as "endocrine disruptors".

WHY THE CONTROVERSY AROUND BISPHENOL A?

In the mid-1990s, one laboratory reported changes in the reproductive tract of male mice whose mothers were fed small (microgram per kilogram per day or μg/kg-day) doses of bisphenol A. Other investigators fed bisphenol A to pregnant mice at the same doses, but they were not able to reproduce the original observations. In a review of the original studies, Ashby (2001) concluded that a lack of attention to "methodological details makes it difficult to reconcile different endocrine disruptor assay outcomes for the

same chemical". From there, the debate escalated (Witorsch, 2002; Purchase, 2004; vom Saal et al., 2005; Purchase, 2005).

Subsequently, research on bisphenol A exploded. By 2007, there were 4,263 published scientific papers on developmental toxicity, acute and chronic toxicity, carcinogenesis, immunotoxicity, neurobehavioral toxicity, genotoxicity, biochemical toxicology, epidemiology studies, studies with workers exposed to bisphenol A and analyses of its concentrations in food, water and soil (summarized in Goodman et al., 2006; United Kingdom Health and Safety Executive, 2007, Willhite et al., 2008).

One reason for the controversy concerns the route of administration. Many of the studies that show adverse effects in rodents given small doses of bisphenol A used subcutaneous injections. Most of the studies in rodents that did not show adverse effects even at high doses used the oral route. Keeping in mind that nearly all (99%) of a child's bisphenol A exposure occurs via ingestion (Wilson et al., 2007), several agencies have published criteria and conclusions on this important point:

- "In routine tests, administration should be by the anticipated route(s) of human exposure. This is logical, since the amount and rate of a chemical that reaches the embryo varies according to the route of administration." (WHO, 1984)
- "The route of exposure in these studies is usually oral, unless the chemical or physical characteristics of the test substance or pattern of human exposure suggests a more appropriate route of administration." (US EPA, 1991)
- "The injection route of administration renders those studies of no utility for quantitative risk assessment as this is not a relevant route of exposure." (CERHR in Boekelheide et al., 2004)

- "Section 6A. Route of Administration. If the population exposure to the chemical entity is by ingestion, then the compound will be administered orally." (Health and Welfare Canada, 1975)

Since 99% of human bisphenol A exposure occurs via ingestion, only those laboratory studies that used the oral route are candidate key studies for human health risk assessment.

SHOULD BISPHENOL A BE BANNED?

Previous experience tells us about public fear of developmental toxins. Nowhere is this more evident than a mother's fear of exposure to therapeutic drugs, pesticides, hair dyes, paints, varnishes, solvents or unidentified, exotic or difficult-to-pronounce industrial or environmental chemicals that could harm her baby (Koren et al., 1989). History also provides us with examples of the actions taken by confused and/or paranoid government agencies, the courts and the popular press that increased public anxiety about developmental toxicants. Unfortunately, these actions increase human misery.

Two examples illustrate that point:

A) In 1973 the US Consumer Products Safety Commission (CPSC) banned the sale of certain spray adhesives and published national warnings that these products caused birth defects and chromosome damage. The CPSC warned all pregnant women who may have had contact with these sprays to see their physician and inquire about the chromosomes of their fetus. The minimum consequences of this action were: 1273 working days

logged by 130 US diagnostic and genetic counseling centers, at least 380 chromosome studies, 11 amniocenteses and at least 9 elective abortions out of concern for exposure to spray adhesives. Eight of these abortions were performed without diagnostic amniocentesis and one was performed in an expectant mother who had chromosome breaks in her amniotic fluid. The genetic counselor in the latter case informed the woman that he was unable to determine the health of her fetus with the information at hand; she elected abortion out of fear of possible birth defects and without telling the counselor of her decision. The aborted fetus was subject to a detailed autopsy. Not only was there no evidence for any abnormality, but the suspected chromosome change was found to be due to viral contamination of the sample. In those areas of the country where local newspapers gave the CPSC announcement the highest visibility, the larger were the numbers of pregnant women who had genetic testing. Six months later, the CPSC withdrew the ban because no toxicity of the substances in the spray could be demonstrated and the original observations on chromosome damage could not be confirmed (Hook and Healy, 1976) [Attachment]. Other examples of the dread instilled in pregnant women by sensational stories and hyperbole (Gunderson-Warner et al., 1990) and the consequences of that fear are well known (Koren et al., 1989; 1993; Trichopoulos et al., 1987).

B) In 1956, a drug known as Bendectin (Debendox) was first marketed to control nausea and vomiting. Its use was very common and 20-25% of all expectant mothers used the drug and a total of 30 million pregnancies were exposed over the 27 years that the drug

was available. The customary dose was 1-4 tablets per day, each containing 1-2 mg/kg-day of the active ingredient.

In the September 1979 issue of *The National Enquirer*, the following appeared:

> "Experts Reveal...Common Drug Causing Deformed Babies. In a monstrous scandal that could be far larger than the thalidomide horror, untold thousands of babies are being born with hideous defects after their mothers took an anti-nausea drug (Bendectin) during early pregnancy."

Then in the November 1980 issue of *Mother Jones* ("The Bendectin Coverup"), the magazine advised pregnant women to use – instead of Bendectin- "natural alternatives" including 100 mg of pyridoxine (a dose 10 times that of the same compound in Bendectin).

As of 1987, at least 300 lawsuits had been filed contending that Bendectin caused birth defects (primarily of the limbs). Given the spontaneous or "background" rate of all types of congenital malformations in the United States (~3%), it would be expected that 900,000 malformed babies would be born to those 30 million mothers even in the absence of Bendectin use. Given the United States background rate for limb defects (1 per 3000 births), 10,000 such defects would be expected in the absence of any Bendectin exposure.

Bendectin does not cause birth defects in animals (including non-human primates), but delayed maturation of the fetal skeleton in laboratory studies can be seen at doses 250-400 times those that were used in clinical medicine. There are at least 14 cohort and 18 case control epidemiology studies on Bendectin in addition to one (conducted by the NIH) in which the occurrence of congenital malformations was prospectively studied in

31,564 newborns. The results of the NIH study, just like those of the others, found the odds ratio for any of 58 major categories of malformations and Bendectin exposure was 1.0 – exactly that expected by chance alone. Of those categories with a 'trend' or 'suggestive' positive associations, the magnitude of those associations was as great as that from vomiting during pregnancy with Bendectin use as without Bendectin use.

Bendectin was withdrawn from the market not because it lacked efficacy or because it caused toxicity, but because of the excessive litigation costs incurred by the manufacturer in defending the drug. Let is also be known that at least 7 women elected to terminate their pregnancies after reading the *National Enquirer* article (reviewed in Brent, 1995).

IS BISPHENOL A SAFE?

To answer that question, one must keep in mind that what is considered "safe" by one person is not necessarily considered "safe" by another person. Therefore, we must re-phrase that question and ask:

What is the Bisphenol A Margin of Exposure?

To determine the relative hazard or safety associated with any chemical in air, soil, food or water, one compares the exposure (measured here as microgram per kilogram of body weight per day or μg/kg-day) for a particular age group or gender to a "tolerable daily intake" (TDI) or a "reference dose" (RfD). The Europeans use the term TDI and the US EPA uses the term RfD, but these are synonyms. The difference between the total

daily exposure and the RfD (or the TDI) is called the "Margin of Exposure". The larger the margin of exposure, the greater the level of safety.

In order to determine the margin of exposure, we need to be able to compare the particular exposure to a "benchmark" value or limit. These limits are exemplified by the Health Advisories and Maximum Contaminant Levels (MCLs) promulgated by State and Federal agencies to control public exposure to contaminants in drinking water. To derive a limit value for bisphenol A, we first need to have an oral reference dose (RfD). After we have our RfD, then we can compare the measured human exposures for that chemical to the RfD. In that way we can calculate the margin of exposure for a particular product, for groups of people with different characteristics or people with different exposure patterns. Margins of exposure differ depending on the specific substance and how people encounter the substance.

WHY IS NSF INTERNATIONAL INTERESTED IN BISPHENOL A?

NSF International is a private not-for-profit public health and safety company. Among its many activities, it offers voluntary certification of various kinds of products after testing those products to rigorous standards. In 1988, US EPA terminated its drinking water additives program and it was replaced by NSF Standards 60 and 61. Among the many products evaluated are those that contact drinking water (e.g., faucets, meters, pipe, valves, and tank liners). As there is no Federal drinking water Health Advisory or Maximum Contaminant Level (MCL) for bisphenol A, NSF conducted a human health risk assessment on bisphenol A so it could be used to facilitate its certification activities.

REFERENCE DOSE

In the United States, the U.S. FDA regulates bisphenol as an indirect food additive (21 CFR 17.105). As noted above, there is no drinking water MCL for bisphenol A and the RfD developed by US EPA was derived in 1987. Using new information, the European Commission (2006) updated its TDI for bisphenol A to 50 μg/kg-day and in 2008, NSF International derived an oral RfD for bisphenol A of 16 μg/kg-day (Willhite et al., 2008) [Attached]. Both the European Commission oral TDI and the NSF oral RfD are based on the audited multi-generation Good Laboratory Practice (GLP) reproduction studies with rats and mice fed bisphenol A (Tyl et al., 2002; 2008). Auditors from the US EPA (OPPT) and the German Federal Institute for Health Protection and Veterinary Medicine found the laboratory facility in which the study was conducted and the rat data complied with Good Laboratory Practice regulations; an external audit of the mouse study was conducted by Toxicology/Regulatory Services (Charlottesville, Virginia) with identical findings.

Differences between the European Commission and NSF results are due to the application by NSF of an 'extra' safety factor of 3 to account for the sparse neurobehavioral and immunologic data and because none of the available studies meet current regulatory testing guidelines (US EPA 1998a; 1998b; 2005).

DIETARY BISPHENOL A EXPOSURE

As more than 99% of a person's exposure to bisphenol A is due to that in the diet (Wilson et al., 2007), there are several studies that have quantified bisphenol A exposure; some were conducted in the United States and others were completed in Europe, Japan, the United Kingdom and New Zealand. Depending upon which study one chooses to use, the results vary up to 1000-fold. This is because some laboratories use an aggregate method (e.g., measuring bisphenol A in representative foods and making estimates about the quantities of each food consumed) and others use biomonitoring (e.g., measuring total bisphenol A metabolites in urine). Each has its advantages and disadvantages. Unfortunately, the overall exposure estimates vary widely and some depend on whether consumption of wine stored in epoxy-lined vats is included or excluded.

For purposes of illustration, only margin of exposure comparisons using data from the United States are given here:

- US FDA (Bailey, 1996) Based on the bisphenol A found in infant formula stored in reusable polycarbonate infant bottles and using the highest bisphenol A concentrations measured in prepared formula from 5 leading U.S. manufacturers marketed in epoxy-lined cans, the U.S. FDA calculated total cumulative infant exposure at not more than 7 μg/child per day to 1 year of age. Based on a 10 kg child, the daily exposure would be 0.7 μg/kg-day. Compared to the European Commission TDI, the margin of exposure is 71x and using the NSF oral RfD, the margin of exposure is 23x.

- The European Commission (2006) tabulated daily dietary exposures to bisphenol A for residents of the United States. In particular, this aggregate analysis found the infant dose depended on the bisphenol A concentration in the particular formula (10 or 50 μg/L) and whether the formula was given in polycarbonate or glass bottles. At the lower concentration in formula, the daily dose for a 3 month infant given formula in a polycarbonate bottle was twice (4 μg/kg-day) that for an infant given the same formula in a glass bottle (2 μg/kg-day). The highest aggregate exposure estimate (13 μg/kg-day) was that for a 6-month-old fed 50 μg/L bisphenol A formula in a polycarbonate bottle. Based on the European Commission TDI, the margins of aggregate exposure are 12, 25 and 4, respectively. Using the oral RfD calculated by NSF International, the margins of aggregate exposure are 4, 8 and 1.2, respectively. However, using results from biomonitoring studies of total bisphenol A metabolites in urine, the European Commission (2006) found daily bisphenol A exposure from all sources was not more than 0.16 μg/kg-day and the margin of exposure is 312x. Using the NSF International oral RfD, the daily margin of exposure is 100x. The discrepancies between the aggregate and the biomonitoring exposure estimates are due to assumptions about the quantity and types of food consumed (European Commission, 2006) and this is reflected in the different margins of exposure.
- Wilson et al. (2003; 2007) studied children living in Durham and Raleigh, North Carolina. These authors accounted for the child's total (aggregate) bisphenol A exposure from all liquids and from all solid foods at home and at daycare (including that from house dust and soil). Average total daily ingested bisphenol

A was 0.043 μg/kg-day (16 times less than the US FDA result). Compared to the European Commission TDI, the margin of exposure for North Carolina children ages 1.5-5 years is 1,162x and compared to the NSF oral RfD, the margin of exposure is 372x.

DRINKING WATER AND BISPHENOL A

The numbers of reports of bisphenol A concentrations in drinking water are far fewer than those reporting bisphenol A levels in food. Three studies were identified: one from Germany (Kuch and Ballschmiter, 2001), one from Japan (Miyamoto and Kotake, 2006) and one in the US (Stackelberg et al., 2004). The drinking water bisphenol A concentrations range from 0.0003 μg/liter to 0.42 μg/liter. Compared to the NSF International Total Allowable Concentration of 100 μg/liter for bisphenol A in drinking water, the margin of exposure ranges from 240x (Stackelberg et al., 2004), to 588x (Miyamoto and Kotake, 2006) to 50,000 to 300,000x (Kuch and Ballschmiter, 2001).

IF NOT A BAN ON BISPHENOL A, THEN WHAT?

Regulatory agencies in North America (US EPA, 2002) and Europe use standard human health risk assessment methods combined with risk management tools to control exposures to a wide range of synthetic and naturally-occurring chemicals. The European Commission and the NSF International human health risk assessments for bisphenol A are based on the same government-audited multi-generation reproduction studies in

rodents. In each assessment, the authors concluded that the results of feeding bisphenol A to mice supported the results of feeding bisphenol A to rats. Differences in the application of a "database uncertainty factor" reduced the reference dose in the NSF analysis compared to reference dose derived by the European Commission.

Margin of exposure values vary depending upon which bisphenol A exposure data are selected for comparison. Some of the smallest margins of exposure (23-71x) are associated with assumptions that: A) an infant consumes one exclusive type (or brand) of infant formula B) all formula contains the highest bisphenol A concentration (6.6 μg/L) measured and C) the formula is given in reusable polycarbonate infant bottles that leach the highest concentration (1.7 μg/L) (Bailey, 1996). The margin of exposure based on the European Commission (2006) ranges from 1 to 312x and the margin for North Carolina children (Wilson et al., 2003; 2007) ranges from 372-1162 x. The drinking water margin of exposure ranges from 240 to 300,000x.

Historically, bisphenol A has been an indirect food additive where it was present in bisphenol A epoxy-lined cans but this has been largely replaced by polyterephthalate films (Miyamoto and Kotake, 2006). Thus, the older U.S. FDA (1996) and the European Commission (2006) aggregate exposure evaluations may overestimate current exposures. If so, current margins of exposure would be greater than those shown above. Given the remarkably broad range in exposure results between the aggregate and the biomonitoring methods, it is obvious that we need accurate quantitative measurements of daily human exposure. Only then can a regulatory agency determine the level of health risk posed by exposure to bisphenol A.

Adoption of an absolute prohibition of bisphenol A-related materials in toys or beverage and food containers uses only on the first step (Hazard Identification) of the National Academy's Principles of Toxicity Assessment. Rather than legislation of an outright ban on polycarbonate plastics in consumer products and bisphenol A-epoxy resins in food and beverage containers, the United States is fortunate to have the US FDA, the US EPA and the US Consumer Product Safety Commission. These agencies all follow the five steps of the process adopted by the National Research Council (1994) and by the Presidential/Congressional Commission (1997): Hazard Identification, Dose-Response, Risk Characterization (which includes Exposure Assessment), Uncertainty Description and Risk Communication. The results of the health risk assessment are used along with risk management factors (e.g., analytical and technical capabilities) in regulatory decision-making.

To address the on-going debate surrounding bisphenol A and public health, we need clear maximum tolerated concentration limits for foods, beverages and - depending upon the results of bisphenol A bioavailability studies - for polycarbonate consumer products. To increase the accuracy of the bisphenol A reference dose, audited GLP studies that meet current regulatory testing requirements (US EPA, 1998a; 1998b; 2005) are needed to address the data gaps. Each of these aspects can be addressed by the respective regulatory Agency using its current rule-making authority.

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Attachments (2)

CALVIN C. WILLHITE, Ph.D.
June 10, 2008
U.S. House of Representatives
Committee on Energy and Commerce Testimony

Bisphenol A Testimony Main Point

Toxicological evaluation and control of public exposure to any material is best handled using procedures outlined by the National Academy of Sciences (NAS). These procedures involve hazard identification, dose-response assessment, risk characterization, risk management and public risk communication. History shows us that legislative and regulatory actions which neglect those steps have created tremendous public health problems in the past.

Since the notion of outright prohibition of any one or another material in commerce is fraught with unintended consequences and the United States is fortunate to have strong regulatory mechanisms in place, the wise course of action is to use the NAS procedures and to direct the regulatory agencies responsible for protection of the public health to promulgate safe limits for bisphenol A in foods, beverages and consumer products

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DERIVATION OF A BISPHENOL A ORAL REFERENCE DOSE (RfD) AND DRINKING-WATER EQUIVALENT CONCENTRATION

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Human exposure to bisphenol A (BPA) is due to that found in the diet, and BPA and its metabolites were detected at parts per billion (or less) concentrations in human urine, milk, saliva, serum, plasma, ovarian follicular fluid, and amniotic fluid. Adverse health effects in mice and rats may be induced after parenteral injection or after massive oral doses. Controlled ingestion trials in healthy adult volunteers with 5 mg d_{16}-BPA were unable to detect parent BPA in plasma despite exquisitely sensitive (limit of detection = 6 nM) methods, but by 96 h 100% of the administered dose was recovered in urine as the glucuronide. The extensive BPA glucuronidation following ingestion is not seen after parenteral injection; only the parent BPA binds plasma proteins and estrogen receptors (ER). The hypothesis that BPA dose-response may be described by a J- or U-shape curve was not supported by toxicogenomic data collected in fetal rat testes and epididymes (after repeated parenteral exposure at 2–400,000 μg/kg-d), where a clear monotonic dose-response both in the numbers of genes and magnitude of individual gene expression was evident. There is no clear indication from available data that the BPA doses normally consumed by humans pose an increased risk for immunologic or neurologic disease. There is no evidence that BPA poses a genotoxic or carcinogenic risk and clinical evaluations of 205 men and women with high-performance liquid chromatography (HPLC)-verified serum or urinary BPA conjugates showed (1) no objective signs, (2) no changes in reproductive hormones or clinical chemistry parameters, and (3) no alterations in the number of children or sons:daughters ratio. Results of benchmark dose (BMD_{10} and $BMDL_{10}$) calculations and no-observed-adverse-effect level (NOAEL) inspections of all available and reproducible rodent studies with oral BPA found BMD and NOAEL values all greater than the 5 mg/kg-d NOAELs from mouse and rat multigeneration reproduction toxicity studies. While allometric and physiologically based pharmacokinetic (PBPK) models were constructed for interspecies scaling of BPA and its interaction with ER, multigeneration feeding studies with BPA at doses spanning 5 orders of magnitude failed to identify signs of developmental toxicity or adverse changes in reproductive tract tissues; the 5-mg/kg-d NOAELs identified for systemic toxicity in rats and mice were less than the oral NOAELs for reproductive toxicity. Thus, it is the generalized systemic toxicity of ingested BPA rather than reproductive, immunologic, neurobehavioral, or genotoxic hazard that represents the point of departure. Using U.S. Environmental Protection Agency (EPA) uncertainty factor guidance and application of a threefold database uncertainty factor (to account for the fact that the carcinogenic potential of transplacental BPA exposure has yet to be fully defined and comprehensive neurobehavioral and immunotoxicologic evaluations of BPA by relevant routes and at relevant doses have yet to be completed) to the administered dose NOAEL results in an oral RfD of 0.016 mg/kg-d. Assuming the 70-kg adult consumes 2 L of water each day and adopting the default 20% U.S. EPA drinking water relative source contribution yields a 100 μg/L BPA total allowable concentration (TAC).

Popular literature, scientific investigation, and legislative activity have been stimulated by concern that exposure to bisphenols, *para*-alkylphenols, and other xenobiotics that interact with steroid hormone receptors contributes to infertility, impaired reproduction, precocious puberty, or endometriosis or produces breast, vaginal, prostate, and uterine cancer (*Consumer Reports*, 2000; Weitzman, 2005; Maffini et al., 2006). In 1996, the U.S. Congress passed the Food Quality Protection Act and amended the Safe Drinking Water Act to require the U.S. Environmental Protection Agencey (EPA) to implement testing/screening strategies for endocrine-active chemicals.

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later, and, as expected (4), actually increase habituation when stimuli are tested immediately after treatment. The experimental design of these short-term experiments consisted of selecting a specimen at random from the stock population, mounting it in the usual manner, testing the habituation rate 1 hour after mounting, then exposing the specimen to intense (100 db) tone pulses for 1 hour, retesting the habituation rate immediately after the treatment, and finally, allowing a 1-hour recovery period and testing again. Individual specimens exhibit increased habituation when tested 2 minutes after treatment (Fig. 1E), but recovery from this short-term depression occurs in 1 hour. Thus, short-term effects are unlikely to influence our results.

Our conclusion is that long-term use of the pathways between the afferent neuron and the giant interneurons during maturation leads to the development of a pathway that is less plastic. We do not know how permanent the effect is, because we have not yet systematically tested at long intervals after removing treated specimens from the stimulus.

It is significant that the change was not a mere increase or decrease in efficacy; no difference was detected when single stimuli were used. Instead, the lability of the system was altered: the habituation curve was not shifted, but its slope was changed.

We have no evidence as yet about the site of the change, but this is a monosynaptic pathway and the postsynaptic cells are accessible for intracellular recording. Hence we feel that this preparation is an excellent candidate for the cellular analysis of a developmental change.

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18 August 1975; revised 14 October 1975

Consequences of a Nationwide Ban on Spray Adhesives Alleged to Be Human Teratogens and Mutagens

Abstract. *A report of an association of chromosome breakage and birth defects with spray adhesive exposure resulted in a ban on the sale of these products and nationwide publicity warning exposed women. Six months later the ban was removed; the association could not be confirmed. Replies to questionnaires sent to medical genetics centers throughout the United States revealed that more than 1100 inquiries had been received and more than 1200 working days were expended because of the issue. Eleven exposed women underwent diagnostic amniocentesis, and one elected to abort her fetus. Eight other women who were exposed also elected to do so, but without first undergoing diagnostic amniocentesis. The episode illustrates some of the unexpected and unnecessary consequences that can arise from the false identification of an environmental agent as a mutagen or teratogen.*

In August 1973, the United States Consumer Product Safety Commission announced a reported association between exposure to some spray adhesives and chromosomal breakage and birth defects. The sale of these products was abruptly banned, and they were recalled from the market (*1, 2*). The Commission widely publicized a warning to all those exposed, particularly pregnant women, and urged them to consult a physician concerning chromosome studies. The ban was withdrawn in 6 months because the purported associations could not be confirmed, and no toxicity of the substances in question could be demonstrated. In fact, the results of reexamination of the original slides by other investigators did not confirm the first interpretation of increased chromosome breakage in those exposed (*3*).

The medical subspecialists for exposed individuals heeding the Commission's advice were primarily the medical geneticists, especially those doing genetic counseling and providing services in cytogenetics. Some centers were reported to have been deluged for requests for counseling and diagnostic services as a result of the Commission's announcements (*1*).

In an attempt to estimate the minimum impact of this episode, we sent questionnaires in May 1974 to all individuals in the United States listed in a national directory (*4*) as providing services both in diagnostic cytogenetics and genetic counseling (Table 1). They were asked to estimate the number of inquiries received, the number of chromosome studies of those who had made inquiries, the total number of working days expended because of this episode, the number of amniocenteses performed, the number of induced abortions, and any other adverse outcomes. They were also asked to comment on any possible beneficial consequences of this episode for those exposed.

There were 190 replies from independent units of which 182 were from active independent centers (Table 1) (*5*). There was a great range in the number of reported inquiries at these centers. More than one-third of the centers reported no inquiries

Table 1. Response categories to questionnaire and inquiries reported by those independent active centers which replied.

Active independent centers reporting	
No inquiries	52
1 to 5 inquiries	68
6 to 10 inquiries	31
11 to 15 inquiries	8
16 to 20 inquiries	8
21 to 25 inquiries	2
> 25 inquiries	7
"Some" inquiries	6
Subtotal	182*
Individuals with collaborative arrangement†	40
Inactive independent centers	8
No reply	5
Total	235

*At the 176 centers reporting an exact number of inquiries, the mean was 6.81 queries. The maximum number of queries reported was 200. The 25, 50 (median), and 75 percent quartile boundaries were 0, 3.2, and 7.6, respectively. The (minimum) total number of queries at these 176 centers was 1198. †Individuals with a separate listing in the directory who are affiliated with an individual at an active independent center from whom a reply was received. See also (*5*).

Table 2. Frequency of chromosome studies at 130 active independent centers receiving inquiries concerning spray adhesives.

Frequency of studies	Centers (No.)
0	49
1 to 5	58
6 to 10	13
11 to 15	4
16 to 20	2
21 to 25	1
> 25	1
"Some"	2*
Total	130
Range	0 to 44
Mean* †	2.97
Quartiles*	
25 percent	0
50 percent (median)	2.0
75 percent	4.2
Total studies (minimum)‡	380

*Those replying "some" were excluded from calculations of mean, quartiles, and minimum total studies. †Standard deviations were not calculated because of the observed skewed distribution. ‡At centers providing exact estimates.

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despite the extensive national publicity. At the 130 centers reporting inquiries, 49 did no chromosome studies (Table 2). A median of 4.6 working days was spent on this issue by the centers reporting inquiries (Table 3).

No direct beneficial effects of this episode for those who were counseled were reported, although one person suggested that an indirect benefit had been to make individuals more aware of genetic counseling services. With regard to other outcomes, a total of 11 amniocenteses were reported from eight centers. In one woman, increased chromosome breakage was reported in cells cultured from amniotic fluid (an observation which may have been due to viral contamination) and an elective abortion was done (6). Three centers reported that they were aware of a total of eight women who, without first undergoing diagnostic amniocentesis, elected to have abortions because of concern about their exposure to spray adhesives.

These data are minimum estimates of the impact of this issue. They do not include results on women who may have consulted family physicians or obstetricians but were not referred to genetic centers. They do not include data from genetic units not listed by the directory (although we are unaware of any, and it seems that the directory lists many inactive individuals), nor do they include the experience of the five centers that did not reply (7). Moreover, there is no estimate of the nature, extent, or consequences of anxieties created by this issue, but we are aware of no ready measure of these.

The centers reporting the greatest number of queries were in Minnesota (where many of the substances were made, and where there apparently was heavy industrial exposure) and, for unexplained reasons, the Pacific Northwest. One respondent noted that a local newspaper had given the issue extensive publicity, which may have prompted many inquiries to his unit. A further study we carried out in New York State suggested that centers receiving no inquiries concerning spray adhesives see fewer patients for genetic counseling of any type than those who reported receiving queries (8). In addition we analyzed the results in a subset of the total of 182 active independent centers: 36 major genetic units known through their publications to be active in genetic counseling. The median (7.5) and mean (16.9) number of inquiries at these were more than double the experience (3.2 and 6.8, respectively) in the total group of 182 active independent centers replying. Only 1 of the 36 major centers reported receiving no inquiries, compared to 52 of the total 182. Thus, at least some of the factors affecting the number of queries

Table 3: Frequency of working days expended at 130 active centers receiving inquiries concerning spray adhesives.

Frequency of working days	Centers (No.)
0	12
1 to 5	54
6 to 10	31
11 to 15	9
16 to 20	2
21 to 25	0
> 25	14
Some	5*
No estimate provided	3*
Total	130
Range	0 to 160
Mean †‡	10.43
Quartiles †	
25 percent	2.4
50 percent (median)	4.6
75 percent	9.4
Total working days (minimum)§	1273

*Of the 130 independent active centers receiving inquiries, there were eight nonrespondents concerning working days of which five reported doing chromosome studies and three did not report any such studies. We have classified the five which reported doing cytogenetic studies as expending "none" working days on this issue. † The calculation of mean, quartiles, and minimum total working days is for the 122 centers providing exact estimates. ‡ Standard deviations were not calculated because of the skewed distribution observed. § At centers providing exact estimates.

received appear likely to be the location of the target population, variation in local publicity, and the size of the referral population of the centers.

Variation in the belief of the evidence cited as supporting toxicity and the extent of the anxiety expressed by the counselees may have contributed to the variation in the total number of chromosome studies, but we have no direct data on this.

The possibility that any substance to which there is extensive population exposure may be teratogenic or mutagenic is, of course, a real one, and the report of suspicion of an effect should be taken seriously. The consequences of the episode reported here, however, illustrate the need to distinguish suspicion of toxicity from evidence for toxicity. If there is nationwide publicity concerning possible mutagenic or teratogenic hazards of a substance, the recent legalization of abortion in the United States and the ready availability of prenatal diagnostic procedures make it likely that many women will avail themselves of amniocentesis (if it appears appropriate to the suspected outcome) and, even in the absence of definitive information, will abort fetuses they believe to be at risk.

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5. Our questionnaire requested that, if two or more affiliated individuals received an inquiry from us, one of them would prepare a summary of their center's experience. In one instance, however, separate replies were received from two individuals apparently affiliated with the same unit, without indication as to whether their reports overlapped. In this case, only the reply of the individual reporting the greater number of queries was included in the tabulations, because of the possibility that the response of the other was a subset of the one tabulated.
6. The genetic counselor informed the mother that, on the basis of this evidence, he was unable to make any specific prediction about the state of the fetus. The mother elected to undergo an abortion, but she did not inform the counselor of this decision until after the procedure, when the abortus had been fixed in formalin. Thus further chromosome studies could not be done. Detailed pathologic examination of the abortus at another institution revealed no evidence for any congenital defect (J. Q. Miller, personal communication).
7. No reply was received from the center at which the association was first reported. It appears likely that extensive work was performed here because of the suspected toxicity of spray adhesives (1–3).
8. Out of a total of 27 active independent genetic counseling centers in New York State who replied, 18 reported receiving inquiries concerning spray adhesives and 9 reported receiving none. In a further investigation 16 of these 18 and 8 of the 9 were able to estimate the number of clients per year they counseled. The mean ± standard deviation (and median) were 204.8 ± 166.1 (175) and 136.3 ± 103.2 (150), respectively, somewhat higher in the group receiving inquiries concerning the adhesives, albeit not significant at the 5 percent level ($P > .3$).
9. We thank those who responded to the questionnaires and M. Hoff for advice on statistical matters.

11 August 1975; revised 7 October 1975

Carotid Body in the Sudden Infant Death Syndrome

Abstract. *Sixty-three percent of victims of the sudden infant death syndrome had a subnormal volume and 23 percent an enlarged volume of glomic cells in their carotid bodies. Evidences of antecedent chronic alveolar hypoxia and hypoxemia were found in both groups but were more severe in the victims with enlarged glomic tissue.*

Prolonged apneic periods during sleep have been described in several sudden infant death syndrome (SIDS) victims prior to death (1, 2). Such apneic episodes may be a common final pathway of death in SIDS. In several adult disorders such episodes of sleep apnea are associated with chronic alveolar hypoventilation (3). Many SIDS victims show characteristic consequences of such chronic hypoventilation,

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Ms. SCHAKOWSKY. Mr. Lester.

STATEMENT OF STEPHEN LESTER, SCIENCE DIRECTOR, CENTER FOR HEALTH, ENVIRONMENT AND JUSTICE, FALLS CHURCH, VIRGINIA

Mr. LESTER. Madam Chair, distinguished members of the subcommittee, thank you for this opportunity to testify on the safety of phthalates and bisphenol-A in everyday consumer products. My name is Stephen Lester, and I am the Science Director with the Center for Health, Environment and Justice. CHEJ is a national environmental health organization founded in 1981 by Love Canal community leader Lois Gibbs. We assist people to fight for justice, empower them to protect their communities, and lead national environmental health campaigns. Phthalates are used to make PVC plastic toys and other PVC products soft and flexible. When children play with or chew on vinyl toys, phthalates can leach out of these products.

As we have heard, phthalates have been linked to reproductive problems during development in both girls and boys. Safe or cost-effective alternatives exist to make soft plastic toys without using phthalates. These alternatives include toys made out of bio-based plastics, polyethylenes, polypropylenes, and ethylene vinyl acetate. In addition, soft plastic toys have been made with non-phthalate plasticizers for years. For example, the Danish company Danisco, one of the largest manufacturers of food additives in the world, introduced a phthalate alternative for toys and other products that has been approved for use in both the EU and in the U.S.

In response to the health hazards posed by phthalates in children's toys, the European Union and many countries around the world have restricted the use of phthalates in children's toys. Prior to the EU's permanent ban, 15 countries from around the world also had banned phthalates in children's toys. The U.S., however, is one of the few developed countries with no government limits on phthalates in toys aimed at young children. Since the EU banned phthalates from toys, toy sales have increased at a pace that exceeds the growth in the United States. Ninety-five percent of all toys sold in the U.S. are manufactured outside of this country, 85 percent in China.

As a result, amendments such as the Feinstein amendment, which has been introduced, won't disrupt the marketplace in the U.S. because we are not exporting or manufacturing very many toys. Many leading toy companies and retailers are already restricting phthalates. Ten years ago, Mattel, Hasbro, and Toys"R"Us, three U.S.-based, multi-national companies who represent 60 percent of all U.S. toy sales, announced they would reformulate their toys globally and take out phthalates to meet the EU toy standards. By early 1999, as we heard earlier, a large number of companies stopped making, I guess it was rattles, teethers, and pacifiers in the U.S. voluntarily. Many of these same companies now are also committed to phase out the production of all toys that include phthalates.

Retailers are also removing toys made with phthalates from their shelves. European retailers and manufacturers have been phasing out phthalates and other toxic chemicals in toys for many years.

We are now seeing a similar movement here in the United States. Over the past 2 years, some of the largest retailers in the U.S., including Wal-Mart, Target, and Sears Holdings have announced policies to phase out and restrict toxic chemicals such as phthalates in children's toys and in products they sell. Phthalates are also being phased out by leading hospital and cosmetic companies across the country. Over 100 health care institutions and nearly 1,000 cosmetic companies have pledged to phase out their use of toxic chemicals such as phthalates.

Bisphenol-A is used in the manufacture of consumer products made out of polycarbonate plastic, which include baby bottles, reusable water bottles, and infant formula containers. Studies conducted on laboratory animals and cell cultures have linked low doses of BPA to obesity, diabetes, thyroid disease, breast, and prostate cancer, and other illnesses. In April of this year, the federal government of Canada proposed designating BPA as toxic under the Canadian Environmental Protection Act, which will lead to a ban on BPA baby bottles and other restrictions. In response, there has been a major market movement and backlash away from BPA among baby and water bottle companies, as well as retailers in both the U.S. and Canada. This includes Wal-Mart, CVS, Toys"R"Us, Playtex, Sears Canada, Home Depot Canada, and many other companies. At the state level, last October California became the first state in the Nation to ban the sale of kids toys with phthalates. Washington State also did this this past year in April.

In total, a dozen states introduced legislation to ban phthalates or BPA from kids' products or child care articles over the past year. These new market trends and the legislative activity in the state should be reinforced by federal legislation. This important issue should not be left only to individual states to legislate. Congress has the opportunity and the responsibility to provide all our children with the same level of protection afforded now to children in only a few states. I respectfully urge the subcommittee to do everything in its power to insure the House includes a ban on phthalates in children's toys and child care articles and the Consumer Product Safety Commission reform pack it will be voting on later this month.

Lastly, I understand that legislation has been introduced today by Representative Markey to ban BPA in food and beverage containers, including baby bottles. This legislation should also be supported. I thank the Committee for this opportunity to testify, and I will try to answer any questions you have.

[The prepared statement of Mr. Lester follows:]

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U.S. House of Representatives Subcommittee on Commerce, Trade and Consumer Protection of the Committee on Energy and Commerce

Hearing on Safety of Phthalates and Bisphenol-A in Everyday Consumer Products

Tuesday June 10, 2008 at 10 am

Stephen Lester, Science Director
Center for Health, Environment and Justice

Summary of Testimony

Phthalates in children's vinyl toys: Phthalates are chemical substances that make PVC (polyvinyl chloride) plastic toys and other PVC products soft and flexible. When children play with or chew on PVC toys, phthalates can leach out of these products. Phthalates have been linked to reproductive problems including shorter pregnancy duration and premature breast development in girls and sperm damage and impaired reproductive development in males.

Safer products are available: Safer cost-effective alternatives exist such as PVC-free toys that are manufactured without phthalates as well as phthalate-free plasticizers. For example, Danisco, one of the largest manufacturers of food additives in the world, introduced a phthalate alternative for toys and other products that has been approved for use in the EU and the U.S.

Phthalates restricted around the world: In response to the health hazards posed by phthalates in children's toys, the European Union and many countries around the world have restricted the use of phthalates in children's toys. Yet, these chemicals continue to be used in our children's toys and baby products here in the United States, making our country literally a dumping ground for potentially unsafe children's products. The U.S. is one of the few developed countries with no governmental limits on phthalates in toys aimed at young children.

The Feinstein amendment would not have adverse effects on U.S. manufacturing: 95% of all toys are manufactured outside of the U.S. - 85% in China and the remaining 10% in Taiwan, Japan or the Philippines. The Feinstein Amendment won't disrupt the marketplace in the U.S. because we're not exporting, or manufacturing very many toys in the U.S. compared to the quantities manufactured in China.

Many leading toy companies and retailers are already restricting these chemicals: Ten years ago Mattel, Hasbro and Toys"R"Us -- US based multinational companies - announced they would globally meet the EU standards. Over the past two years, some of the United States largest retailers including Wal-Mart, Target, Sears Holdings (Sears and Kmart), and Toys"R"Us have announced major policies to phase out or restrict toxic chemicals such as phthalates and/or PVC in children's toys and infant products.

Background on BPA: Bisphenol A is a chemical that's used to manufacture polycarbonate plastic. BPA is used to make polycarbonate consumer products including baby bottles, reusable water bottles, and infant formula containers. Studies conducted on laboratory animals and cell cultures have linked low doses of BPA to obesity, diabetes, thyroid disease, breast cancer, prostate cancer and other illnesses.

Canadian ban on bisphenol A: In April 2008, the federal government of Canada proposed to designate BPA as "toxic" under the Canadian Environmental Protection Act which will lead to a ban on BPA baby bottles and other restrictions.

Retailer response to Canadian government announcement: Since the Canadian government has proposed to designate BPA as "toxic", there's been a major market movement and backlash away from BPA among baby and water bottle companies as well as retailers in both the U.S. and Canada. This includes Wal-Mart, CVS, Toys"R"Us, Nalgene, Playtex, Sears Canada, Home Depot Canada, and many other companies.

U.S. state action on Phthalates and BPA: In the absence of federal action, an increasing number of U.S. states are introducing legislation to ban phthalates and bisphenol A.

Mr. Chairman, distinguished Members of the Subcommittee, thank you for this opportunity to testify on the safety of phthalates and bisphenol A in everyday consumer products. My name is Stephen Lester and I'm the Science Director for the Center for Health, Environment and Justice (CHEJ). CHEJ, a national environmental health organization founded in 1981 by Love Canal community leader Lois Gibbs, assists people to fight for justice, become empowered to protect their communities from environmental threats and leads national environmental health campaigns. I thank the members of the subcommittee for this opportunity to testify today.

My testimony today will focus on the growing market shift away from phthalates and bisphenol A in consumer products such as children's toys, as well as the increasing attention these chemicals are receiving from U.S. states and internationally. Over the past-three years, we have worked with leading U.S. retailers to phase out phthalates and BPA in consumer products.

Phthalates in Children's Toys & Other Consumer Products

Phthalates in children's vinyl toys: Phthalates are chemical substances that make PVC (polyvinyl chloride) or vinyl plastic soft and flexible. Between eighty to ninety percent of all phthalates are used to soften or plasticize PVC products. Phthalates are also used in other consumer products such as cosmetics, although again the vast majority are uniquely used to soften vinyl plastic products. Among many other things, phthalates are used in soft PVC toys and other baby products, such as teething rings, rubber duckies, and bath books. They're also used in other products such as vinyl shower curtains, flooring, wall coverings, medical devices (i.e. IV bags) and many other PVC products. Phthalates can leach out of these toys and other products over time, making children's natural behavior - exploring their world by putting things in their mouths - especially concerning.

The dangers of phthalates: Phthalates have been linked to reproductive problems including shorter pregnancy duration and premature breast development in girls and sperm damage and impaired reproductive development in males. They've been shown to be harmful at even low levels of exposure. The many small doses of phthalates from a myriad of products adds up to a much bigger exposure, particularly since it's understood that different phthalates in combination can have additive or synergistic effects. Additionally, the timing of chemical exposure to infants and children, who are changing and developing every day, may be as important as the dose.

Safer products are available: Safer cost-effective alternatives exist such as PVC-free toys that are manufactured without phthalates as well as phthalate-free plasticizers.

You can make soft toys without PVC plastic and without phthalates. Safer alternatives to PVC baby / children's products and toys include toys made out of biobased plastics, polyethylenes, polypropylenes, thermoplastic elastomers, and ethylene vinyl acetate (EVA) that are free of phthalates. These plastics do not require the use of phthalates since some are naturally softer, but many PVC products cannot be made without a plasticizer such as phthalates. The PVC-free plastics listed above also pose fewer lifecycle hazards because they are not chlorinated and do not release dioxins and furans during manufacture and disposal and are manufactured with chemicals that are less hazardous.

Additionally, you can manufacture PVC with non-phthalate plasticizers that have been used to soften toys for years. For example, a Danish company Danisco, one of the largest manufacturers of food additives in the world, introduced a phthalate alternative for toys and other products that has been approved for use in both the EU and the U.S.

Phthalates restricted around the world: In response to the health hazards posed by phthalates in children's toys, the European Union and many countries around the world have restricted the use of phthalates in children's toys. The European Union has banned DEHP, DBP, and BBP in all toys and childcare articles and banned DINP, DIDP, and DNOP in toys and child care articles that can be put in the mouth. Prior to the EU's permanent ban, the following countries also had banned phthalates in children's toys: Argentina, Austria, Cyprus, Czech Republic, Denmark, Fiji, Finland, Germany, Greece, Italy, Japan, Mexico, Norway, and Sweden. In many other countries, governments have requested voluntary industry action to remove phthalates. In some cases industry has voluntarily removed phthalates, and governments have issued health advisories related to phthalates.

In response, the major multinational toy manufacturers responded by reformulating toys to remove toxic phthalates. Yet, these chemicals continue to be used in our children's toys and baby products here in the United States, making our country literally a dumping ground for potentially unsafe children's products. This double standard is unacceptable, and may be putting children at risk of toxic chemical exposure. The U.S. is one of the few developed countries with no governmental limits on phthalates in toys aimed at young children.

The Feinstein amendment would not have adverse effects on U.S. manufacturing: Rep. Diane Feinstein introduced an amendment to the CPSC reform bill that would ban phthalates in children's toys sold in the U.S. Because so few toys are manufactured here in the US - 85% are of the toys sold in the U.S. are manufactured in China and the remaining 10% in Taiwan, Japan or the Philippines – this amendment would not have adverse effects on U.S. manufacturing. As evidenced by last year's wave of recalls on lead-contaminated toys, these countries have poor oversight of toxic chemicals such as lead and phthalates in children's products. Only a small percentage of high-end specialty toys are actually manufactured in

either the U.S. or Europe. The Feinstein Amendment won't disrupt the marketplace in the U.S. because we're not exporting, or manufacturing very many toys in the U.S. compared to the quantities manufactured in China. Meanwhile, the rest of the developed world banned phthalates from toys starting a decade ago and the toy-manufacturing world responded by reformulating toys to remove toxic phthalates.

As a result, Chinese manufacturers are now making one set of "safe toys" for EU consumption and the same manufacturers are making "toxic toys" that they are dumping on the U.S. because no one else will buy them. So while transnational companies in the U.S. can demand their manufacturing plants in China build phthalate-free toys, companies selling only in the U.S. have no pressure to do so. A simple internet search reveals a long list of manufacturers – some of which are producing phthalate-free toys that are compliant with the EU directive, and some of which are not– proving it is possible for the very same manufacturer to produce a toy with phthalates or one without phthalates. Given the number of phthalate free toy manufacturers that have emerged throughout the world one could easily argue we've not only not seen a market disruption, but instead the opposite has occurred: the world market has been stimulated to produce safe alternatives. For instance, since the EU banned phthalates from toys, toy sales have increased, at a pace that exceeds their growth in the United States. Banning phthalates in the U.S. could potentially create new research and job opportunities in the field of green chemistry to produce safe alternatives.

Many leading toy companies are already restricting these chemicals: A number of leading baby and children's toys manufactures such as Brio, Chicco, Evenflo, First Years, Gerber, International Playthings, Lamaze Infant Development, Lego Systems, Sassy, and Tiny Love have committed to phase out all PVC toys including and prioritizing those containing phthalates. Other toy manufacturers such as Discovery Toys and Manhattan Baby have committed to

phase out phthalates and some PVC toys. Additionally, many of the largest toy companies including Hasbro and Mattel are in compliance with the European Union ban on phthalates in children's toys both globally and in the United States. Ten years ago Mattel, Hasbro and Toys"R"Us -- US based multinational companies - announced they would globally meet the EU standards.

Retailers are phasing out toxic chemicals in toys: European retailers and manufacturers have been phasing out phthalates and other toxic chemicals in toys for many years. Over ten years ago, European retailer Ikea phased out all PVC toys including those containing phthalates and switched to safer plastics.

We are now beginning to see similar movement in the United States. Over the past two years, some of the United States' largest retailers including Wal-Mart, Target, Sears Holdings (Sears and Kmart), and Toys"R"Us have announced major policies to phase out or restrict toxic chemicals such as phthalates and/or PVC in children's toys and infant products. These initiatives are summarized below.

Toys"R"Us' phthalate and PVC policy: In 2008, Toys"R"Us announced that by the end of 2008, all juvenile products must be produced without the addition of phthalates. The company is reducing PVC use and is moving towards a goal of offering PVC-free toys, toys that would also be phthalate-free.

Target's phthalate and PVC policy: Target has agreed to systematically reduce its use of PVC and phthalates in children's products. The company has committed to phase out phthalates in most of their toys by Fall 2008. They eliminated phthalates in all baby-changing tables by January 2008. The company is reducing PVC (and therefore phthalates) found in many of its

owned brand products including infant products, children's toys, shower curtains, packaging and fashion accessories. Target children's eating utensils and lunchboxes are now PVC-free (and therefore phthalate-free). Target baby bibs became PVC-free (and therefore phthalate-free) as of January 2008.

Wal-Mart's phthalate and PVC policy: Wal-Mart most recently announced they are requiring suppliers to significantly limit phthalates in children's products. They have also required suppliers to phase out PVC (and therefore phthalates) in children's lunch boxes, baby bibs, packaging, and beginning to address PVC used in building materials and electronics. The company also supports an industry-wide standard to remove PVC (and therefore phthalates) from all products intended for kids.

Sears and Kmart's PVC policy: Sears Holdings (Sears and Kmart) has announced it is working to reduce and phase out PVC (and therefore phthalates) in its packaging and merchandise including children's toys. Sears is working to identify safer, more sustainable and cost-effective alternatives to PVC and incorporate them into the design and manufacturing process for their private label merchandise and packaging.

Phthalates and cosmetics: Over five hundred cosmetics companies have pledged to get toxic chemicals such as phthalates out of cosmetics. Some phthalates have already been banned in cosmetics in the European Union, but like toys, are still legal in the U.S.

Phthalates and health-care: A growing number of hospitals are undertaking efforts to reduce phthalates and PVC use in their facilities. Health care organizations are changing their purchasing practices to eliminate phthalates including Kaiser Permanente, Catholic Healthcare

West, Consorta, and Premier. From 2010, all medical devices in the European Union will have to be labeled if they contain the phthalate DEHP.

U.S. state action on phthalates: In the absence of federal action, an increasing number of U.S. states are introducing legislation to ban phthalates in children's toys. California became the first state in the nation last year to ban phthalates in toys, recently the states of Washington and Vermont followed suit. These states are not alone. Similar legislation has been introduced in 2008 in other states including Connecticut, Hawaii, Maryland, Illinois, Massachusetts, Minnesota, New Jersey, New York, and West Virginia.

Global chemical companies are shutting down phthalate production: In response to this major market shift, even chemical manufacturers are phasing out phthalate production. For example, the German chemical giant BASF shut down its European DEHP production after the EU ban in 2005 became permanent. Now, BASF produces a new and profitable plasticizer line called DINCH - after spending five million euros on safety testing - which can be used in toys, food-contact materials and medical applications. In the U.S. however, BASF continues to manufacture DEHP in two facilities in Pittsburgh, PA and Texas City, Texas for consumer product uses in the American market.

Growing support for banning phthalates in the U.S. Eighty-seven legislators from 28 states—all members of the National Caucus of Environmental Legislators—have signed on to a May 19 letter to the conferees in support of the Feinstein amendment. In addition, 60 organizations have stated their support for the amendment in a May 27 letter to legislators.

The response from the U.S. chemical Industry: Exxon Mobil, who manufactures DINP, has spent more than $3 million to lobby against both the proposed federal – and state – bans on

phthalates in children's toys - and other issues - in the first three months of 2008. Exxon Mobil alone has four outside lobbying firms registered to fight the phthalates ban. The irony here is that Exxon Chemicals manufactures products that are phthalate free -- metallocene polyolefins.

Bisphenol A (BPA) in Consumer Products

Background on BPA: Bisphenol A is a chemical that's used to manufacture polycarbonate plastic. BPA is used to make polycarbonate consumer products including baby bottles, reusable water bottles, toddler sippy cups, infant formula containers, food-can linings, dental sealants, compact discs, DVDs, and other consumer products.

Dangers of BPA: BPA is a synthetic sex hormone that's been linked to serious diseases at low doses of exposure. Studies conducted on laboratory animals and cell cultures have linked low doses of BPA to obesity, diabetes, thyroid disease, breast cancer, prostate cancer and other illnesses. BPA exposure is widespread and has been found in 95% of Americans tested including in breast milk.

Canadian ban on bisphenol A: In April 2008, the federal government of Canada proposed to designate BPA as "toxic" under the Canadian Environmental Protection Act. In declaring BPA toxic, government officials expressed concern that infants are exposed to bisphenol A at levels that could cause health effects. They are proposing a number of actions: to ban polycarbonate baby bottles; to develop stringent migration targets for bisphenol A in infant formula cans; to work with industry to develop alternative food packaging and develop a code of practice. Canada is now the first national jurisdiction to consider designating bisphenol A as 'toxic' to human health and the environment, and to begin implementing regulation on the use of this

chemical. In the fall 2008, the government will publish a final assessment recommendation and a risk management approach to regulating bisphenol A.

Retailer response to Canadian government announcement: Since the Canadian government proposed to designate BPA as "toxic", there's been a major market movement and backlash away from BPA among baby and water bottle companies as well as retailers in both the U.S. and Canada. These actions are summarized below.

Wal-Mart, CVS, Toys"R"Us phasing out BPA: U.S. retailers Wal-Mart, CVS, and Toys"R"Us have announced plans to phase out BPA-contaminated baby bottles.

Playtex eliminates BPA-contaminated baby bottles: Playtex has announced they will replace infant feeding products made with BPA with a BPA-free material by the end of 2008.

Nalgene and BPA: Nalgene, a company that has been a staunch defender of BPA in recent years, announced they will phase out BPA in water bottles they sell and has already begun to sell many BPA-free safer products.

Canadian retailers and BPA: In December 2007, two major Canadian-based retailers, Mountain Equipment Co-op and Lulemon, announced they would stop selling BPA-laden water bottles. In 2008, Sears Canada, Wal-Mart Canada, Rexall Pharmacies, London Drugs and Home Depot Canada announced they would remove plastic baby bottles, reusable water bottles and other products made with bisphenol A (BPA) from their shelves. Sears Canada announced it has removed from sale baby products and sport bottles which contain bisphenol A and are designed to come into direct contact with the mouth. Other Canadian companies removing

BPA-contaminated products include Canadian Tire, the Forzani Group Ltd., and Hudson's Bay Company.

Canadian grocery distributors and BPA: Members of the Canadian Council of Grocery Distributors also announced they will stop selling all polycarbonate baby bottles in April 2008. Members include Canada Safeway Limited, Colabor, L.P., Colemans Food Centre, Co-op Atlantic, Costco Wholesale Canada Ltd., Flanagan Foodservices Inc., Federated Co-operatives Limited, GFS Canada Company, H.Y. Louie Co Limited, Jean-Paul Beaudry Ltd., the Kitchen Table Incorporated, Loblaw Companies Limited, METRO INC., Neate Roller Limited, Sobeys Inc., Summit-Cambridge, SYSCO Foodservices of Canada Inc., Tannis Food Distributors, Thrifty Foods – Sobeys Inc., and Wallace & Carey Inc.

Whole Foods cuts BPA Baby bottles: Whole Foods, the nation's largest natural foods chain, stopped selling baby bottles and child drinking cups made from polycarbonate plastic.

Eden Foods eliminating BPA in food can linings: In 1999, the health foods company Eden Foods phased out the use of BPA in some of their canned foods. The company has eliminated BPA in cans for products such as beans, however they are still searching for alternatives for cans that hold tomatoes.

U.S. state legislative initiatives on BPA: A growing number of U.S. states have introduced legislation to ban bisphenol A. These include California, Connecticut, Hawaii, Illinois, Maryland, Massachusetts, Minnesota, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont.

EU and BPA: In response to the growing scientific consensus that BPA is bad for our health, and recent market shifts, the European Union's food safety agency is planning on reevaluating the safety of BPA in food and beverage applications.

Conclusion

Major retailers and manufacturers in the United States and around the world are already phasing out these unnecessary toxic chemicals in children's and infant toys in favor of safer products. These new market trends should be reinforced by federal legislation such as the Feinstein Amendment, to ban phthalates in children's products. Legislation introduced by Senator Schumer (D-NY) to ban bisphenol A should also be supported. Additionally, more comprehensive legislation is urgently needed to reform our nation's outdated chemical policies and get toxic chemicals out of everyday consumer products such as children's toys and baby bottles.

Thank you for the opportunity to testify.

About The Center for Health, Environment & Justice

CHEJ mentors a movement building healthier communities by empowering people to prevent harm through programs focusing on different types of environmental health threats. CHEJ works with communities to empower groups by providing the tools, direction, and encouragement they need to advocate for human health, to prevent harm and to work towards environmental integrity. Following her successful effort to prevent further harm for families living in contaminated Love Canal, Lois Gibbs founded CHEJ to continue the journey. CHEJ has assisted over 10,000 groups nationwide.

Currently, CHEJ is mentoring community groups in several states including Florida, Maryland, New Jersey, New York, North Carolina and Ohio. Details on CHEJ's efforts to help families and communities prevent harm can be found at http://www.chej.org.

Ms. SCHAKOWSKY. Thank you. We will begin our questioning now, and I will begin with myself for 5 minutes. Ms. Stanley, you state that it is a myth that phthalates are used for teething rings, and yet Mr. Lester, in your written testimony I was listening for, I am not sure you said it, states that phthalates are used in teething rings, so now that we have both of you here, I am wondering if you could first state how you know that, what is used instead of phthalates.

Ms. STANLEY. Certainly, I can answer that question. There have been a couple of voluntary agreements that the toy industry has had with removing some phthalates. The first was in the early 1980s, and that was DEHP. There was the threat of rodent liver cancer. There was a voluntary agreement, now part of an ASTM standard, that limited that phthalate to 3 percent in teethers, rattles, and pacifiers.

Ms. SCHAKOWSKY. Is that only for U.S. manufacturers?

Ms. STANLEY. Yes. That is for U.S. manufacturers.

Ms. SCHAKOWSKY. So it could be imported. It could be in teething rings that are imported?

Ms. STANLEY. I wouldn't imagine that because I know that the toy industry association from my discussions with them has very strict standards, and they enforce those standards with their manufacturers overseas, particularly in Asia. Now the second part of a restriction was with DINP, and as Dr. Babich from CPSC discussed, that was in the late '90s. Now I don't know what has been substituted, but once the market shifts away, that shift will pretty much remain permanent. I have not had discussions with the toy industry association. I know they support the continued use of DINP because of all the reviews and their certainty that it is safe to use with children.

Ms. SCHAKOWSKY. OK. Mr. Lester.

Mr. LESTER. Well, I can't speak to this specifically, but it is my understanding that because so many of the toys are imported now that there is no control or oversight over which of these contain or not contain phthalates.

Ms. SCHAKOWSKY. OK. You do speak to it specifically in your testimony saying that among other things phthalates are used in soft PVC toys and other baby products such as teething rings, rubber duckies, and bath books.

Mr. LESTER. Well, what I am referring to there is that these are products that are imported into the United States. It is my understanding that, yes, phthalates are included in these products.

Ms. SCHAKOWSKY. OK. Let me ask another question. In former testimony, I think it was Dr. Babich saying that when testing how children actually mouth various things, it said that it was lower than expected, and that the greatest amount was on their fingers, and I am just wondering if there is the possibility of harm done because of sucking on their fingers and if anybody here has any data on that, whether it is transferable. Dr. Schettler.

Dr. SCHETTLER. I published a paper on human exposure to phthalates from consumer products, and in the process of doing the research for that paper tried to wrap my head around figuring out where the phthalates come from, if anybody really knows. And as Dr. Gray mentioned in the previous panel, sometimes people are

identified with high levels but we don't know where they came from because these chemicals are so ubiquitous. But one conclusion does seem to be gaining consensus in the scientific world, and that is that dust contamination with phthalates is probably an important pathway for children because of hand to mouth activity, and that is based on both doing dust analyses in homes and then measuring phthalate metabolites in the urine of children.

You begin to see a correlation there that holds up for children, but not for adults particularly well, so the conclusion drawn is that general environmental contamination, dust contamination, and hand-to-mouth activity is an important exposure pathway, which then of course sets the stage for the sucking on the toy or the other sources. That DINP or whatever phthalate is coming from the toy is not coming into an empty child. A child already has a background level of phthalates. That is why this mixture conversation is important.

Ms. STANLEY. And, Madam Chair, we do have data on the absorption of phthalates through both living rat skin and through human cadaver skin, and we know that DEHP in particular has a very, very low absorption rate. Additionally, in response to some reviews by the cosmetic ingredient review, an independent scientist did some work on the absorption of dibutyl phthalates through the nail bed because that phthalate isn't really used in vinyl. It is used more in cellulosic type plastics, so we have got that data as well, which we would be happy to provide to you.

Ms. SCHAKOWSKY. I would appreciate that. Given Dr. Bucher's testimony that the National Toxicology Program maintains that BPA poses some concern, that is the mid-level of concern, to infants and children, will the American Chemistry Council revisit its position on the safety of BPA?

Ms. STANLEY. I would like to refer that to my colleague, Dr. Hentges.

Ms. SCHAKOWSKY. Would you introduce yourself?

Mr. HENTGES. Sure. I am Dr. Steven Hentges. We are in the process of reviewing that report ourselves. In fact, I think as you heard earlier, there is a meeting tomorrow at which the NTP Board of Scientific Counselors will review that report as well. Once everything is finalized, we will certainly take a close look. One of the things we will be taking a very close look at is what additional research has been recommended. There is quite a bit that was recommended in that report. And, in fact, we have one study underway now. It is completely independent from the NTP report, but one study underway now that will address one of those scientific needs, so that is in particular one of the areas that we will take a look at very closely.

Ms. SCHAKOWSKY. OK. Let me see if I have any time. I do. Oh, it is not. OK. I am out of time. Sorry. Mr. Whitfield.

Mr. WHITFIELD. Well, I would also like to thank this panel of witnesses. Mr. Lester, I was reading an article on Forbes Magazine, and it said that the president of a company called Born Free came and talked to Children's Health and Environmental Justice, a group of people from there. Is that the name of your organization?

Mr. LESTER. Not precisely, no.

Mr. WHITFIELD. So it is not the same. Did he speak to your group at all?

Mr. LESTER. No, he did not.

Mr. WHITFIELD. Well, anyway in this article it talks about how he expressed concern about BPA and said that it included arsenic, for example, and as a result that and other information was ever convinced, whole foods and others to move away from BPA, and yet it is my understanding that there isn't any entity anywhere in the world that has banned the use of BPA. Is that correct or is that not correct, Ms. Stanley?

Ms. STANLEY. That is correct.

Mr. WHITFIELD. But, Dr. Schettler, you and Mr. Lester, would I be inaccurate to say that you have real concerns about BPA, is that correct?

Dr. SCHETTLER. I have real concerns about BPA for two reasons. First, because the exposures are ubiquitous in the population. From a public health perspective, that really wakes me up, and it wakes most people up. When you have population-wide exposures, and you have population-wide exposures in fetuses and infants, now you really start to pay attention from a public health perspective. Second, when you see these low dose effects that are showing up in the animal literature even though, as we have heard, there is uncertainty and disagreement about how to interpret the data, you still have from my perspective as a public health professional, I am quite concerned about that because if these effects are happening in people we have set the stage for an epidemic of disease that we are going to be living with for decades.

Mr. WHITFIELD. Dr. Willhite, what do you think about BPA?

Mr. WILLHITE. Sir, I think the question that you are probably asking in a shorthand way is, is BPA safe or not? That ought to be the kind of question—what it really boils down to is what we call the margin of exposure, and I am going to give you one example to illustrate what that is and will pick kids in daycare and at home that have been followed. The important thing to understanding about this is the larger the margin of exposure, the more comfortable you should be. For example, that is why we have like a drinking water limit, and then you can compare the results of your studies measuring it in drinking water with a margin of exposure. For myself, this is my personal opinion, I like to see at least a margin of exposure about 10 times lower than what my number is. Say if your drinking water maximum at that level, you don't really want to be right at the number. You want to be a little bit less or hopefully a lot less.

If we look at the drinking water number, the concentrations that have been measured around the world and in the United States, the margin of exposure there is between 200 and 300,000, so I wouldn't worry too much about drinking water. Let us go over to our daycare kids, and these are kids that were living in Durham and Raleigh, North Carolina. The references are Wilson 2003 and 2007. These authors accounted for the child's total aggregate bisphenol-A exposure from all liquids and from all solid foods at home and at day care, and they included dust and soil. Average total daily ingested bisphenol-A was 0.043 micrograms per kilogram a day. Compared to the European, like the bench mark num-

ber, the margin of exposure for North Carolina children ages 1½ to 5 years is 1,162, and compared to the NSF oral RFD, they are a little bit different; the margin of exposure is 372.

So what you want to please do in your considerations is to look at different margins of exposure and the one that you are going to want to focus on the most, and if it is safe for this particular group, that group is the smallest margin of exposure is for the premature infant given formula. But we need more accurate estimates on the real range of bisphenol-A exposures in that population because they vary for two reasons. One is the way they calculate exposure through bio monitoring. They measure the amount of metabolites in urine, and then back-calculate to what it was that you ate. The other is you go and you measure all the different kinds of foods there are, and you measure how much is in there. Then you figure out how much red chili pepper you eat, and how much of this or that or the other, and then they add them up. The problem, each has its advantages, each has its disadvantages, but when you are in a decisionmaking situation, the problem is that the uncertainty in the exposure estimate is off by 1,000.

So now you are stuck with this uncertainty, and that is just how it is. But from the best data that we have, that is the most—that is the critical population you want to look at, and the others are on the order between 200 and 372 and nothing at all.

Mr. WHITFIELD. Thank you.

Ms. SCHAKOWSKY. Ms. Hooley.

Ms. HOOLEY. Thank you, Madam Chair. Thank you for testifying. Dr. Schettler, I have a couple of questions for you. One is, you know, why does exposure to phthalates in toys and children's articles matter? Isn't the dose too small to worry about? Some of the witnesses today have argued that there is plenty of evidence to be concerned about kids' exposures to phthalates, and other witnesses argue just the opposite. What, in your opinion, should be the role of policymakers when confronted with a lack of consensus within the scientific community and/or scientific uncertainty around this issue?

Dr. SCHETTLER. Thank you for the question. There are really two parts to it. The reason that I am concerned about phthalates in toys is because of the aggregate exposure issue. I mean if you just take a toy and calculate the DINP, for example, as we heard that is leaching out and do a risk assessment based on that, that is one thing, but if you do it in a real world set of circumstances where children are already contaminated with other phthalates, but as we have heard other non-phthalate chemicals that act in an additive fashion, that is the real world risk assessment that we ought to be thinking about. That DINP from that toy is going into a context that is not clean.

The other part of your question is a very interesting and important one, having to do with how do policymakers deal with uncertainty, and I think it is a very important thing to think about. We should think about necessity of products. We should think about alternatives to products, and we should think about how our policy decisions can actually drive us toward a safer material market. One of the things that struck me today is that we are being told that because we are ignorant about certain other plasticizers that

we ought to continue with the status quo. What this is really doing is rewarding ignorance. The fact that we have products on the market containing chemicals whose toxicity has not even been investigated is being used as a reason for maintaining the status quo with chemicals that we have concern about.

We really ought to be formulating policies that are going to drive us to more information and to a safer, material market. So I think in this set of circumstances we have heard that there are alternative plastics, there are alternative materials as well as alternative plasticizers. We could pick out from this whole constellation of products that contain either bisphenol-A or phthalates and think about which ones that we might want to restrict in some way. I mean if you restricted bisphenol-A in baby bottles because dietary exposure is an important exposure and this is important for these infant kids, there are plenty other materials that you could make baby bottles out of that wouldn't pose any of this risk because they don't have materials that are leaching out in the same way.

We have to think creatively about how to deal with uncertainty in a way that both doesn't create new risks and also drives the market into safer material.

Ms. HOOLEY. Thank you. I have a follow-up question. What do you think of the CPSC stating they just looked at DINP?

Dr. SCHETTLER. The one that was described earlier today?

Ms. HOOLEY. Yes.

Dr. SCHETTLER. Well, again, I think that it was a traditional CPSC risk assessment that was based on the assumption that the child who is sucking on that toy does not have pre-exposure to any phthalates, and then they did an analysis and came up with their conclusion. But we know from the scientific literature that DINP does interfere with testosterone synthesis similar to the other five phthalates that have been mentioned, and although I would agree that it is not as potent as the others, it has been shown that it is additive. And so we need to do our risk assessments in a much more real world way where we are looking at the real context in which these children live when we are deciding about the additional hazard posed by this particular product under these circumstances.

Ms. HOOLEY. Thank you very much. Dr. Lester, in your testimony you argue that alternatives exist to PVC toys softened with phthalates, but many members of this subcommittee have been visited by representatives of the toy industry that argue there are no alternatives, and kids will choke and die from chewing on or playing with hard plastics. I am confused. What has Europe been using in the last decade since their ban on phthalates in toys went into effect, and what are some of the alternatives to the phthalates we have been discussing today that can be used to make toys soft?

Mr. LESTER. Well, there are alternatives on the market, and I think the European Union example is the best example of that because they have had this ban in place since 2005, and earlier a number of companies voluntarily moved away from it. And so they are selling toys over there, and they are doing quite well. They are selling more there than we are here. So there are alternatives, and some of these alternatives include some of the alternative plastics such as polyethylenes, polypropylenes. There is a whole new area

now of development in these bio-plastics that are using corn and other forms of natural components to create plastic. And so there are these alternatives. They exist. They can be used. There are also others that don't use plasticizers at all.

So I think there is a good track record of these alternatives, and I think you just have to look for them and you have to—and people are using them so there is a track record.

Ms. HOOLEY. One quick follow up. The policy of restricting use of phthalates in toys, people have said would disrupt the U.S. market. Is this something we need to be worried about?

Mr. LESTER. I am sorry. I didn't hear the first part.

Ms. HOOLEY. A lot of people say that if you don't use phthalates in toys that it would disrupt the U.S. market, and my question is, is this something we need to be worried about?

Mr. LESTER. I don't think so. I mean it is important not to disrupt the U.S. market certainly, but given the small amount of toys at least that are made here in this country, 95 percent are imported, and there is no regulation on those coming in. So if we set a ban here on what the U.S. companies are manufacturing in this country or put restrictions on it, it won't have very much of an impact unless it also applies to those toys being imported.

Ms. STANLEY. Ms. Hooley, may I have a comment, please, on that. I might be able to shed some light here. One of the reasons that vinyl is a useful plastic is that it can be customizable, if you will, by the amount of plasticizer. And I have been on conference calls with small to medium toy industries. These aren't the Mattels and the Hasbros of the world. These are the people who are designing prototypes of toys. These are the people who are making a small part because of this year's fashionable doll they can provide a certain piece of it. And when the fashion changes, as it does yearly in the toy industry, they can quickly change to another part. I have heard medium-size manufacturers say we will have to stop making some parts because we don't have the R&D because changing to an alternate plasticizer isn't a one-to-one switch-off.

You have got to change some stabilizers. You have got to change some other things. And so I have personally heard these folks say on the phone that is the impact of them.

Ms. HOOLEY. Thank you.

Ms. SCHAKOWSKY. Ms. DeGette.

Ms. DEGETTE. Thank you. Well, just to reassure you, Ms. Stanley, if we ever did change the standard, we wouldn't do it overnight. Congress can't possibly move that quickly, so it would be some period of time for manufacturers to adjust. Mr. Lester, something you just said was really telling to me, and I think something we have to deal with as policymakers is it does—I mean we are all here to try to improve the lives of our constituents and consumers, and so the solution here really wouldn't be just to ban the use of these substances in toys manufactured in the United States because as you point out, the vast majority of toys are now imported, and that is why we have to really think about the risk and what we are going to do in general.

And that is, I think, why the large toy manufacturers, as I was fleshing out with the last panel with Dr. Babich, I think the reason the large toy manufacturers voluntarily stopped putting DINP into

toys is because they couldn't sell their toys internationally and in other countries where they have stronger standards. And so don't you think we would need to have stronger standards for all toys that are distributed in the United States, not just toys that are manufactured in the United States?

Mr. LESTER. Oh, without question. The market has changed such. The global economy is such that it has to be——

Ms. DEGETTE. And what we are trying to think about globally in terms of our consumer product legislation that is in the conference committee right now is we are trying to think about how we structure our statutes to deal with the shifting markets where we have so many imports coming in. Dr. Schettler, I wanted to follow up on a couple questions Ms. Hooley was asking you about because it is hard for us as policymakers to grapple with scientific studies and differing conclusions. What you are saying is that these studies that the CPSC is relying on are really studies that were based on—that didn't look at the environmental data of these children and infants, correct?

Dr. SCHETTLER. That is correct.

Ms. DEGETTE. And what you are saying is that there are other studies that you are relying on that when you look at the environmental factors there really were much more serious health hazards than the studies that the CPSC is relying on?

Dr. SCHETTLER. Well, what I am saying is that I don't make the assumption that the child, the theoretical child in the risk assessment, is empty of phthalates before sucking on the toy.

Ms. DEGETTE. Now what about Ms. Stanley's statement that the phthalates, at least certain types of them, do not in the industry's opinion get absorbed through the skin?

Dr. SCHETTLER. Well, I wasn't commenting on skin absorption. I do have opinions about skin absorption, but I was just simply saying that we can take a sample of children and take urine from them and measure phthalates in them. The Centers for Disease Control has done this, so we know that children are contaminated with mixtures of phthalates in the real world.

Ms. DEGETTE. OK. Not just through skin absorption.

Dr. SCHETTLER. Not just through skin absorbtion. From all sources.

Ms. DEGETTE. OK. I thought it was interesting, and I am thinking about this from a policy-making standpoint what Dr. Babich told me about, and actually this would be for you, Mr. Lester, as well, about what it would take for the Consumer Product Safety Commission to actually ban phthalates in these toys, and he went through all of the standards that we have at the CPSC. The industry did voluntarily leave DINP out, but my question is if you go through all of the CPSC standards and the current status of the scientific data, do you think that the threshold would be met under current law to have the CPSC ban these?

Mr. LESTER. No, for the same reasons that Dr. Babich concluded. It is unlikely because the authorizing legislation is so onerous that you need to demonstrate significant evidence of harm and do a cost benefit analysis, and he named all the——

Ms. DEGETTE. Do you think these are the correct standards that we should be looking at, these substances and consumer products?

Mr. LESTER. No, clearly not protective of public health.

Ms. DEGETTE. Do you think these standards are more protective of industry than they would be of consumers?

Mr. LESTER. Well, they clearly protect the product and the product manufacturers. That is perhaps even what they were intended to do, but from a public health perspective the burden of proof is on the public or the legislature or the regulators to demonstrate harm, which is really not where it ought to be. Now the Food and Drug Administration in the pharmaceutical program has a different burden of proof and a different set of thresholds that they need, but not in the Consumer Product Safety Commission.

Ms. DEGETTE. When were those CPSC standards promulgated? Was it in the original enacting legislation for the CPSC?

Mr. LESTER. I would assume so, but I am not an expert on that legislation.

Ms. DEGETTE. My time has expired, but I am wondering if you, Mr. Lester, Dr. Willhite, and Ms. Stanley, any of you would be willing to supplement your testimony with any recommendations you may have as to how we could modify the CPSC standards to be more in line with protecting consumers. Thank you. Thank you, Madam Chair.

Ms. SCHAKOWSKY. I want to thank everyone. I would without objection just ask one more question of Ms. Stanley. Do you have any doubts about the safety of phthalates, and what would it take for you to be convinced that they are unsafe?

Ms. STANLEY. Well, I have managed this group, and I have seen them through research. I am coming up on 19 years now, so I have seen a lot of research conducted. I have seen the industry work as hard to develop just data that doesn't make it look any worse or any better at any of the phthalates. I wouldn't be convinced because I know that they don't bio-accumulate. I know that they have a very quick transit in the body. I know that they look like vegetable oil. We metabolize them like vegetable oil. There are a lot of other things in my life that I would worry about before I worried about a phthalate.

Ms. SCHAKOWSKY. Yes. No, go ahead. Mr. Whitfield has one more comment as well.

Mr. WHITFIELD. I am really perplexed by this hearing in the fact that the data seems so strong in so many ways. And, Mr. Lester, you and Dr. Schettler, you make the argument that there are alternative materials that can be used. They obviously are using them in Europe and whatever. These materials that are being used today have been used for 40 or 50 years. They have undergone all sorts of tests. Now can you categorically say with certainty that the substitute material that would be used instead of phthalates would not pose any harm to health in any way to young children or anyone else in our society?

Dr. SCHETTLER. Well, just a couple of quick comments. As Ms. Stanley has said, the substitute depends on the application, so it is not just a drop in substitute. For example, there are alternatives to phthalates that used to be used in food wraps that are no longer used in food wraps, and now there are substitutes that have been well studied and considered to be far safer.

Mr. WHITFIELD. Scientific studies.

Dr. SCHETTLER. Lots of scientific studies.

Mr. WHITFIELD. And now they are being used in Europe today.

Dr. SCHETTLER. But what I don't know is because I am not a material scientist whether or not those same phthalates could be used in toys. In other words, you have two choices here. You can either use an alternative plasticizer or you can use an alternative material, and I think those rubber duckies there tell that story. One has phthalates because it is probably made out of vinyl that requires phthalates. The other is made out of an alternative material that doesn't require a plasticizer, so there are different ways to approach the alternative question.

Mr. WHITFIELD. If you know, I mean even in the European Union after they banned this, they came back and did another study and concluded that they were safe, but because of the politics of it, they didn't want to go back. And I mean all of us are exposed to all sorts of things in our environment that may be harmful to us, and this item may be totally safe but other things may be harmful to us, and it seems to me that these particular substances that we are discussing specifically today are no more unsafe than a lot of other things that we are exposed to. And I think that we do have to look at the cost and the potential health that we have with substitutes.

Dr. SCHETTLER. With respect, the characterization that the EU went back and re-examined it and determined they were safe is not my characterization, and I don't think it is entirely accurate. It has been stated that way, but I don't think it is entirely accurate. It has been stated that way though.

Mr. WHITFIELD. I was reading an article here that says that.

Dr. SCHETTLER. Yes, there are lots of descriptions about why the EU continued their ban, but as it was mentioned in the previous panel, they believed that there was significant enough risk associated with it despite the uncertainties, that they could and did, in fact, continue to keep phthalates out of toys without disrupting their toy market, and undoubtedly have reduced exposures in kids.

Mr. WHITFIELD. Thank you.

Ms. SCHAKOWSKY. I want to thank the panel, and I would like to ask for unanimous consent for inclusion of a statement by Chairman Dingell. Without objection, that will be included. That concludes our hearing, and I appreciate the testimony very much.

[Whereupon, at 12:50 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

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OFFICE OF CONGRESSIONAL AND
INTERGOVERNMENTAL RELATIONS

The Honorable John Dingell
Chairman
Committee on Energy and Commerce
U.S. House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

I'm responding to your letter dated August 8, 2008, to Dr. L. Earl Gray, Research Biologist, in the Environmental Protection Agency's (EPA) Office of Research and Development regarding questions for the record that followed the June 10, 2008 hearing on "Safety of Phthalates and Bisphenol-A in Everyday Consumer Products." Although Dr. Earl Gray did not testify as an EPA witness, enclosed is his response.

If you have further questions, please give me a call or your staff may contact James Blizzard of my staff at (202) 564-1695.

Sincerely,

Christopher P. Bliley
Associate Administrator

Enclosure

Responses to Questions from August 8, 2008
Honorable Bobby Rush and
Honorable Joe Barton
U.S House of Representatives
Committee on Energy and Commerce

From: Dr. Leon Earl Gray, Jr.
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Disclaimer: The following responses reflect the scientific opinion of Dr. Leon Earl Gray, Jr. and are based upon his assessment of the current state of the science. They do not necessarily reflect the policy of the U.S. Environmental Protection Agency (EPA).

Questions from the Honorable Bobby L. Rush:

Q1. Summarize the harmful effects of phthalates in children.

There are no definitive studies showing that phthalates have "harmed" children. However, studies have not examined the long-term effects of early exposure to phthalates in humans, and "the absence of evidence is not evidence of absence."

There are a few studies that have reported effects of phthalates on children. These studies demonstrate an association between phthalate levels with effects in children. These "associations" correlate exposure with effect, but they do not prove that phthalates caused effects in children. Many of the studies that I listed below are controversial, and I have not attempted to review these here or report "negative" studies (that failed to find an association of phthalates levels and effects in children). Inclusion does not indicate that I fully agree with the author's conclusions. Each study has some limitations and some are controversial. The text below is paraphrased from the abstracts of the papers and is the opinion of the authors of the paper.

Studies correlating phthalate exposure with effects in children

Study 1. Association of phthalate exposure and reduced anogenital index.

One study found a negative relationship between anogenital index (AGI: presumably a masculine trait dependent upon male hormones) and other genital measurements with prenatal phthalate exposure in humans (Swan SH, Main KM, Liu F, Stewart SL, Kruse RL, Calafat AM, Mao CS, Redmon JB, Ternand CL, Sullivan S, Teague JL; Study for Future Families Research Team. Decrease in anogenital distance among male infants with prenatal phthalate exposure. Environ Health Perspect. 2005 Aug;113(8):1056-61. Erratum in: Environ Health Perspect. 2005 Sept.; 113(9): A583). They reported that urinary concentrations of four phthalate metabolites [monoethyl phthalate (MEP), mono-n-butyl phthalate (MBP), monobenzyl phthalate (MBzP), and monoisobutyl phthalate (MiBP)] were inversely related to AGI. They concluded that their data supported the hypothesis that prenatal phthalate exposure at environmental levels can adversely affect male reproductive development in humans.

Studies 2a, 2b and 2c. Association of phthalate exposures and asthma symptoms and "wheezing."

Study 2a. Epidemiologic studies in children show associations between indicators of phthalate exposure in the home and risk of asthma and allergies (Jaakkola JJ, Knight TL; The role of exposure to phthalates from polyvinyl chloride products in the development of asthma and allergies: a systematic review and meta-analysis. Environ Health Perspect. 2008 Jul.; 116(7): 845-53). They reported that studies in children (n = 5) showed an association between PVC surface materials in the home and the risk of asthma [fixed-effects model: summary odds ratio (OR), 1.55; 95% confidence interval (CI), 1.18-2.05; four studies] and allergies (OR, 1.32; 95% CI, 1.09-1.60; three studies). The authors also concluded that heated PVC fumes possibly contribute to development of asthma in adults.

Study 2b. Kolarik et al (2008) reported an association between phthalates in dust and allergic diseases among Bulgarian children (Kolarik B, Naydenov K, Larsson M, Bornehag CG, Sundell J. The association between phthalates in dust and allergic diseases among Bulgarian children. Environ Health Perspect. 2008 Jan;116(1):98-103). Dust samples from the child's bedroom were collected. A total of 102 children (2-7 years of age) had symptoms of wheezing, rhinitis, and/or eczema in preceding 12 months (cases), and 82 were nonsymptomatic (controls). The dust samples were analyzed for their content of dimethyl phthalate (DMP), diethyl phthalate (DEP), di-n-butyl phthalate (DnBP), butyl benzyl phthalate (BBzP), di(2-ethylhexyl) phthalate (DEHP), and di-n-octyl phthalate (DnOP). A higher concentration of DEHP was found in homes of case children than in those of controls (1.24 vs. 0.86 mg/g dust). The concentration of DEHP was significantly associated with wheezing in the preceding 12 months ($p = 0.035$) as reported by parents. The authors reported dose-response relationship between DEHP concentration and case status and between DEHP concentration and wheezing in the preceding 12 months.

Study 2c. Another study reported associations between persistent allergic symptoms in children and the concentration of phthalates in dust collected from their homes (Bornehag CG, Sundell J, Weschler CJ, Sigsgaard T, Lundgren B, Hasselgren M, Hägerhed-Engman L. The association between asthma and allergic symptoms in children and phthalates in house dust: a nested case-control study. Environ Health Perspect. 2004 Oct;112(14):1393-7). They concluded that phthalates, within the range of what is normally found in indoor environments, are associated with allergic symptoms in children. This investigation was a case-control study nested within a cohort of 10,852 children. From the cohort, they selected 198 cases with persistent allergic symptoms and 202 controls without allergic symptoms. They found higher median concentrations of butyl benzyl phthalate (BBzP) in dust among cases than among controls (0.15 vs. 0.12 mg/g dust). Analyzing the case group by symptoms showed that BBzP was associated with rhinitis ($p = 0.001$) and eczema ($p = 0.001$), whereas di(2-ethylhexyl) phthalate (DEHP) was associated with asthma ($p = 0.022$). Furthermore, dose-response relationships for these associations are supported by trend analyses. The authors believe that the different associations of symptoms for the three major phthalates-BBzP, DEHP, and di-n-butyl phthalate-can be explained by a combination of chemical physical properties and toxicological potential. Given the phthalate exposures of children worldwide, the results from this study of Swedish children MAY have global implications.

Studies 3a and 3b. Association of phthalate exposures and precocious puberty in girls.

Study 3a. Girls who were exposed to higher levels of DBP and DEHP than normal children were found to have early onset of puberty (based upon the volume of the uteruses and ovaries measured by ultrasound). (Qiao L, Zheng L, Cai D. [Study on the di-n-butyl phthalate and di-2-ethylhexyl phthalate level of girl serum related with precocious puberty in Shanghai]Wei Sheng Yan Jiu. 2007 Jan;36(1):93-5. Chinese.). The concentrations of two phthalates (di-n-butyl phthalate, DBP, di-2-ethylhexyl phthalate, DEHP) in the serum of 110 precocious girls and 100 normal children were measured by using gas chromatography, at the same time, the volumes of the uteruses and ovaries for precocious girls and normal children were measured by B-ultrasound. DBP and DEHP were detected for 27.3% and 22.7% in precocious girls respectively, DBP and DEHP were detected for only 4% and 3% in normal children respectively. Uterine and ovarian volumes were larger in precocious girls than those of normal children respectively ($P < 0.05$, $P < 0.05$). DBP in serum of precocious girls was correlated with the volumes of the uteruses ($r = 0.456$, $P < 0.05$), and ovaries ($r = 0.378$, $P < 0.01$). DEHP in serum of girls with precocious puberty was correlated with the volumes of uteruses ($r = 0.382$, $P < 0.05$), and ovaries ($r = 0.689$, $P < 0.01$). (This information is from the abstract and the paper is in Chinese so I have not read it, only the abstract: LEG).

Study 3b. In 2000, another study suggested a possible association between plasticizers and premature breast development in girls (Colón I, Caro D, Bourdony CJ, Rosario O. Identification of phthalate esters in the serum of young Puerto Rican girls with premature breast development. Environ Health Perspect. 2000 Sep;108(9):895-900.). The authors reported that Puerto Rico had the highest known incidence of premature thelarche (the start of breast development at the onset of puberty) ever reported. They analyzed 41 serum samples from thelarche patients and 35 control samples. No pesticides or their metabolite residues were detected in the serum of the study or control subjects. Significantly high levels of phthalates [dimethyl, diethyl, dibutyl, and di-(2-ethylhexyl)] and its major metabolite mono-(2-ethylhexyl) phthalate were identified in 28 (68%) samples from thelarche patients. Of the control samples analyzed, only one showed significant levels of di-isooctyl phthalate. The phthalates that we identified have been classified as endocrine disruptors. It has been noted however, that the high levels of parent phthalates (DEHP, for example) suggest possible contamination of samples since one would expect the parent phthalates to be metabolized to the monoesters (MEHP, for example) in the gut.

Study 4. Association of phthalate exposures and early delivery-shorter pregnancies.

Human exposure to DEHP begins in utero and levels have been associated with shorter pregnancy duration (Latini G, De Felice C, Presta G, Del Vecchio A, Paris I, Ruggieri F, Mazzeo P. In utero exposure to di-(2-ethylhexyl)phthalate and duration of human pregnancy. Environ Health Perspect. 2003 Nov;111(14):1783-5.). The investigators measured serum DEHP and MEHP concentrations in the cord blood of 84 consecutive newborns by high-performance liquid chromatography. They found detectable cord blood DEHP and/or MEHP concentrations in 88.1% of the samples. Either DEHP or MEHP was present in 65 of 84 (77.4%) of the examined samples. Mean concentrations of DEHP and MEHP were 1.19 +/- 1.15 microg/mL [95% confidence interval (CI), 0.93-1.44, range = 0-4.71] and 0.52 +/- 0.61 microg/mL (95% CI, 0.39-0.66, range = 0-2.94), respectively. MEHP-positive newborns showed a significantly lower gestational age compared with MEHP-negative infants ($p = 0.033$). Logistic regression analysis indicated a positive correlation between absence of MEHP in cord blood and gestational age at delivery (odds ratio = 1.50, 95% CI, 1.013-2.21; $p = 0.043$).

Study 5. Degradation of phthalate tubing and deep vein thrombosis in children.

Five children with catheter-related deep venous thrombosis were encountered in a pediatric intensive care unit (PICU) (Danschutter D, Braet F, Van Gyseghem E, Hachimi-Idrissi S, Van Bruwaene B, Moloney-Harmon P, Huyghens L. Di-(2-ethylhexyl)phthalate and deep venous thrombosis in children: a clinical and experimental analysis. Pediatrics. 2007 Mar;119(3):e742-53. Epub 2007 Feb 26.). Three types of polyvinyl chloride tubing for the administration of intravenous solutions were in use (Terumo, Codan, and Perfusend). All were di-(2-ethylhexyl)phthalate plasticized. The authors suspected problems with the Codan tubing. Different types of tubing at different time intervals in vitro were investigated. Tubing segments were assessed on structural alterations by surface electron microscopy. High-performance liquid chromatography-diode array detection and liquid chromatography-mass spectrometry-diode array detection were performed to identify and to quantify di-(2-ethylhexyl)phthalate. Surface electron microscopy demonstrated that the Codan tubing's inner surface was severely altered, showing large particles (34.5 +/- 6.1 microm). High-performance liquid chromatography documented that all Codan samples showed a peak at the di-(2-ethylhexyl)phthalate retention time. The analysis of the minimal clinical data set for total catheter-related deep venous thrombosis showed an unusual high incidence in 2001 (52) compared with the expected 36 per year. The authors concluded that disintegration of intravenous tubing resulted in intravenous administration of debris that produced catheter-related deep venous thrombosis and that a considerable number of patients might have been exposed to di-(2-ethylhexyl)phthalate.

Q2. Do phthalates affect children of different ages differently?

It is reasonable, based on available evidence, to assume that children of different ages would be affected differently by exposure to a toxic chemical, because of the unique developmental events taking place during different life stages. For example, reduced anogenital index (AGI) genital malformations, and undescended testes are conditions that could be induced only from exposure during development. However, the hypothesis that phthalates affect children of different ages has not been rigorously studied, to my knowledge. A few studies have reported that the associations among phthalate exposures and effects on humans differed by age group. In the rat, it is well known that the testes of adults are insensitive to phthalates as compared to those during fetal and pubertal life stages.

I have cited one study below that reports on age-related differences in the toxicity of phthalates among different age classes. This study reported that obesity was associated with phthalate levels in older people but not children. This study demonstrates an association between phthalate levels with obesity effects in adults but not children. The text below is paraphrased from the abstract of the paper.

Study 1. Phthalate exposures and obesity.

Hatch et al. (2008) analyzed associations between six phthalate metabolites measured in urine and body mass index (BMI) and waist circumference (WC) in National Health and Nutrition Examination Survey (NHANES) participants aged 6-80. The study included 4369 participants from NHANES 1999-2002, with data on mono-ethyl (MEP), mono-2-ethylhexyl (MEHP), mono-n-butyl (MBP), and mono-benzyl (MBzP) phthalate; 2286 also had data on mono-2-ethyl-5-hydroxyhexyl (MEHHP) and mono-2-ethyl-5-oxohexyl (MEOHP) phthalate (2001-2002). The most consistent associations were in males aged 20-59; BMI and WC increased across quartiles of MBzP (adjusted mean BMI = 26.7, 27.2, 28.4, 29.0, p-trend = 0.0002), and positive associations were also found for MEOHP, MEHHP, MEP, and MBP. In females, BMI and WC increased with MEP quartile in adolescent girls (adjusted mean BMI = 22.9, 23.8, 24.1, 24.7, p-trend = 0.03), and a similar but less strong pattern was seen in 20-59 year olds. In contrast, MEHP was inversely related to BMI in adolescent girls (adjusted mean BMI = 25.4, 23.8, 23.4, 22.9, p-trend = 0.02) and females aged 20-59 (adjusted mean BMI = 29.9, 29.9, 27.9, 27.6, p-trend = 0.02). There were no important associations

among children, but several inverse associations among 60-80 year olds. (Hatch EE, Nelson JW, Qureshi MM, Weinberg J, Moore LL, Singer M, Webster TF. Association of urinary phthalate metabolite concentrations with body mass index and waist circumference: a cross-sectional study of NHANES data, 1999-2002. Environ Health. 2008 Jun 3;7:27.)

Q3. Summarize the state of the science on phthalate mixtures and how this changes the state of the science regarding phthalate use.

State of the Science: the science that is emerging from studies in our laboratory on how mixture of phthalates demonstrates several concepts.

1. Several phthalates disrupt reproductive development of the male rat similarly, whereas other phthalates produce different responses.
2. So far, in our studies we have been able to predict many of the phthalates that would disrupt reproductive development by their structure and it appears that the phthalates that disrupt reproductive development in utero are also the ones that disrupt pubertal male rat development.
3. The effects of mixtures of phthalates produce cumulative reproductive effects. The cumulative effects can be predicted mathematically using a toxic equivalency approach or dose-addition modeling. The information for these predictions is derived from dose response data on the individual phthalates. (Howdeshell *et al.* 2008a; Howdeshell *et al.* 2007a).
4. When phthalates are combined with pesticides that affect reproductive development of the male rat in utero these mixtures also produce cumulative effects that have been predicted mathematically using a toxic equivalency approach or dose-addition modeling. (Gray *et al.* 2006; Hotchkiss *et al.* 2004; Rider *et al.* 2008).

How will this change the state of the science regarding phthalate use?

How the science on the cumulative effects of phthalates affects the use of these chemicals will depend upon how much, if any, the assessment of the cumulative toxicity of these chemicals changes the risk assessment. For example, if risk assessors find that the cumulative and aggregate exposures to all of the chemicals included in a "cumulative effects group" still results in an adequate margin of exposure, then phthalate use would not likely be impacted.

Question from the Honorable Bobby L Rush

Q4. What are the current uses of phthalates in children products?

More often than not this information is not available on any systematic basis to the public or the scientific community so our knowledge here is equivocal. The information that is available indicates that children may be exposed to phthalates from some toys, baby products (lotions and creams), enteric coatings on medications and nutraceuticals, medical tubing and other medical devices, and house dust, for example.

Phthalates in toys.

Different phthalates have been used in a variety of toys; however, it is not always evident which phthalate a product contains and the formulation may have changed over time. For example, DEHP was once used in very high concentrations in pacifiers and baby products http://www.greenpeace.org/raw/content/usa/press-center/reports4/this-vinyl-house.pdf, but it is reported that is not the case at the present time.

Other toys reported to contain phthalates at one time or another include glow sticks and glow products (DBP), modeling clay

http://www.uspirg.org/home/reports/report-archives/toy-safety/toy-safety-reports/hidden-hazards-health-impacts-of-toxins-in-polymer-clays), rattles, and etc. http://www.vpirg.org/documents/TnT07.pdf.

Since some phthalates have been banned by the European Union for several years, many of the websites advertise 'DBP-' or 'phthalate-free' children's products http://www.glowwithus.com/other/about.htm, implying that at one time these products may have contained phthalates.

In the US, several companies have removed phthalates from modeling clay (see CA Prop 65 consent judgment 07B-161, Oct 2007). For example, dihexyl phthalate, a reproductive toxicant in young rats, was removed from modeling clay by the California EPA in 2007.

To the best of my knowledge, specific and up-to-date information on phthalate content of toys and other children's products could only be obtained from the manufacturers or possibly from the Consumer Product Safety Commission (CPSC).

Q5. Are you aware of replacements for phthalates in various children's products?

There are several different kinds of plasticizers, phthalates being one class of these. Among the plasticizers and the phthalates the physical properties vary and different plasticizers have different applications since they impart different physical characteristics to the product. Specific information on the use of different phthalates in these products and useful alternatives is beyond my expertise. This information could most likely be obtained from a product chemist that works with plasticizers in consumer products or possibly from the Consumer Product Safety Commission (CPSC).

Q6. Why did you select nine phthalates for your research including DEHP, BBP, DBP and DINP that are addressed by certain legislation but not DIDP or DNOP which also are included in the legislation?

Our research on mixtures of phthalates and pesticides was initiated in 2002, well before any of the legislation was proposed. We selected the phthalates and pesticides that we have studied to date in order to test several hypotheses about their ability to disrupt sexual differentiation in the rat in utero and how they behave in mixtures.

We selected DEHP, BBP, DBP and DINP because we suspected that they would all reduce fetal male rat testosterone levels and induce reproductive tract lesions in male offspring, with DINP being less potent than the other three phthalates. We included DEP, as a suspected negative, since it is the phthalate that many humans are exposed to at higher levels than other phthalates.

We did not select DIDP or DNOP in our initial fetal exposure studies because DIDP and DNOP are not known to be reproductive toxicants in male rats. We do plan to add these in the future along with several other suspected positives and negatives. Although we have not studied the effects of DNOP on reproductive development we have collaborated on some studies with the Centers for Disease Control and Prevention on metabolism of DNOP (Calafat *et al.* 2006b; Silva *et al.* 2005).

Even though DIDP and DNOP are not known to be reproductive toxicants in the male rat they were included in the European Union legislation because they induced effects on the liver and reduced litter sizes. DIDP and DNOP also are not currently used in toys, according to the European Union risk assessments (EU- DIDP 2003: http://ecb.jrc.it/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/SUMMARY/didpsum041.pdf). However, the European Union added them to the list of restricted phthalates based upon the conclusion that if they were used as replacements for other phthalates then the exposure levels could exceed acceptable margins of exposure (summarized with links to European Union Risk Assessment documents at http://www.greenfacts.org/phthalates/dinp-didp/l-3/6-health-risks-humans.htm#2).

The initial hypotheses of our research that resulted in selection of the phthalates we have studied to date were:

1. Can we predict the reproductive toxicity of phthalates in utero based upon their chemical structure and are these the same phthalates that affect the testis of the young, pubertal age male rat?
2. What are the relative potencies for these phthalates for disrupting sexual differentiation?
3. Can we predict how these phthalates will interact with one another and with pesticides or other toxic substance when administered as mixtures based upon dose response information about each individual chemical?

Potential future mixture studies.

Future studies should expand the list of phthalates that we studied to include several more suspected as "positive" or "negative" for reproductive toxicity, including DIDP and DNOP. Future studies are contingent upon the availability of the chemical (some phthalates are difficult to obtain).

If should be noted that there are additional difficulties associated with studying some of the phthalates like DINP and DIDP. These chemicals are mixtures and different formulations vary. Different formulations may have different CAS numbers and the developmental toxicity of these different formulations of phthalates also can differ (Hellwig *et al.* 1997). In this regard, a comprehensive study of one of these mixtures would actually require assessment of the reproductive toxicity of several different formulations.

We also recommend phthalate mixture studies include new chemicals from other chemical classes, like pesticides and dioxin-like chemicals.

Now that we have found some significant reproductive effects in the female, it is important to characterize these effects further and determine if female effects are induced via the same mode of action as are the male effects. We would like also to know if the effects of phthalates on female sexual differentiation behave as they did in our studies on male rat sexual differentiation .

Q7. The American Chemical Council questions the validity of phthalates research conducted on rodents and points instead to research done on primates, which show different results. Can you explain to us why you think your research using rodents is valid for predicting potential effects in humans?

In the follow discussion I will first review the literature on the developmental effects of phthalates in primates. These studies indicate that the results seen in primate studies are not all negative or inconsistent with the results of studies with rodents.

In the second part of this discussion I will review why it is reasonable to conclude that the in utero effects of phthalates in the male rat are relevant to humans. My conclusion is based upon guidance provided by the EPA in the reproductive risk assessment guidelines (http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=2838).

Effects of Phthalates in Primate versus Rodent studies

Our studies (Howdeshell *et al.* 2007b; Howdeshell *et al.* 2008b) in rodent models show that some of these phthalates reduce fetal testosterone production in rats which in turn results in latent reproductive tract malformations; many of which are not obvious until after the animals reach full maturity. Even in the most severely malformed males the effects are not obvious at birth. I am not aware of any studies in primates that have examined fetal androgen (male hormone) levels after in utero exposure during sexual differentiation or the offspring exposed to phthalates in utero after they reach maturity, which is required to produce the most severe effects in rats. It is noteworthy that DBP

in utero also produces reproductive toxicity in the rabbit, a nonrodent species (Higuchi *et al.* 2003; Veeramachaneni 2008).

DEHP effects in neonatal marmosets

Studies with primates exposed to phthalates during development have shown reproductive alterations as a consequence of DEHP treatment. They are not all negative. One study examined the effects of DBP and its active metabolite MBP on neonatal marmoset testosterone (Hallmark *et al.* 2007). Hallmark et al. (2007) found that in newborn (Day 2-7) marmosets, administration of a single dose of 500 mg/kg MBP significantly ($p = 0.019$) suppressed blood testosterone levels 5 hr later. Similar treatment of newborn co-twin male marmosets for 14 days resulted in increased Leydig cell volume per testis ($p = 0.011$), compared with co-twin controls. They concluded that their findings suggest that MBP/DBP suppresses steroidogenesis by fetal-type Leydig cells in primates as in rodents.

Reproductive effects of phthalates in mammalian species including primates during puberty

Since the phthalates that affect in utero reproductive development in the rodent also are the phthalates that affect pubertal development in rodents it is important to note that phthalates produce testicular toxicity in young male hamsters, ferrets, and guinea pigs and peripubertal DEHP treatment alters reproductive development in pubertal female marmosets. Treated female marmosets showed increased ovarian and uterine weights and elevated blood estradiol level in the 500 and 2500 mg/kg dosage groups versus controls and the increased ovarian weights were associated with the presence of large corpus luteum in the ovary (Tomonari *et al.* 2006).

There are problems with using primate species like the marmoset for developmental and reproductive toxicity studies. For example, in a study of the effects of DEHP on male and female marmosets Tomonari et al (2006) found that a high percentage of animals succumbed to "wasting syndrome" including animals from the control groups. Furthermore, the variance in reproductive measures is often so large that it is difficult to obtain statistical significance even when large effects are seen. In order to obtain statistical significance with such variable data investigators would have to use much larger sample sizes than used in most primate studies, one that would not likely be possible or desirable with a primate species.

The results of the endocrine analyses in the study of the effects of DEHP on the pubertal marmoset are quite variable and even though Tomonari *et al.* (2006) conclude that there are no DEHP-related effects in male marmosets, this could be due to the use of small sample sizes coupled with the large variability in reproductive measures in this species. For example, serum testosterone is reduced in a dose related manner during puberty but this hormone is so variable that a reduction from 7.6 ng/ml in control to 0.6 ng/ml in high dose DEHP treated animals is not statistically significant at week 26. This may result from the fact that the statistical power of this study is such that the probability of detecting a dose related effect of DEHP on testosterone is only 5%, meaning 19/20 times you would report the effect as not treatment-related when in fact it was a treatment related effect.

In addition, Tomanari reported that one male of 6 to 7 males in each treated group displayed reduced testes, epididymal, seminal vesicle and prostate weights, but this also was not considered treatment related. In contrast, in a multigenerational study of DEHP (NTP DEHP RACB) where they used more rats per dosage group, similar incidences of testis lesions were determined to be treatment related because they were statistically significant as a result of the enhanced statistical power. In summary, one must be cautious when they interpret "negative" studies for the reasons discussed above.

Why are studies with rodents relevant to potential human effects of in utero exposure to phthalates?

The pathway that phthalates disrupt in the fetal male rat is highly conserved in all mammals and is known to be critical for human reproductive development. There is no indication that this is a species specific mechanism of action; therefore, there is no scientific evidence supporting the hypothesis that the mode of action altered in rodents is not similar in humans.

In addition, since the molecular pathways that are disrupted that lead to pregnancy loss in rats and malformations of the female rat reproductive tract are not known one cannot assume that these effects also are not relevant to humans.

The pathway disrupted by phthalates in the fetal male rat is known as sexual differentiation.

- In utero, some phthalates disrupt sexual differentiation in rats
- Prior to sexual differentiation in all mammals, including humans, the fetus has the potential to develop as either male or female, having both reproductive duct (tract) systems.
- Normally, in the male the fetal testis produces hormones and these hormones cause the male tract to develop and the female tract to regress.
- In the female, the absence of these hormones causes the male tract to regress and the female tract develops.
- These testis hormones include androgens, antimullerian duct hormone and insulin-like 3.

Human reproductive development in utero is abnormal when the androgen signaling pathway is disrupted (Quigley *et al.* 1995). For example, congenital abnormalities of sexual differentiation in boys are seen in -

- **Androgen Insensitivity syndrome, complete to partial demasculinization**
  - Abnormal androgen receptor – can respond to the hormone.
- **Gonadal dysgenesis**
  - Abnormal testis differentiation – absence or reduced testis hormones.
- **5 alpha reductase deficiency**
  - Males lack an enzyme in reproductive tract and are unable to produce a potent androgen DHT necessary for normal tissue development and function.
- **Abnormalities of testosterone synthesis – complete to partial demasculinization due to reduced androgen levels**
  - Cytochrome P450,CYP11A, 3B-Hydroxysteroid Dehydrogenase, Cytochrome P450,CYP17, and 17-Ketosteroid Reductase Deficiencies.
- **Timing Defects delaying the normal onset of testosterone production in the fetal male**
  - All of the steps required for male sex differentiation are working; yet if these steps are delayed by even a few weeks, the result can be ambiguous differentiation of the external genitalia in a 46,XY individual.
- **Others**
  - Klinefelter's syndrome, genetic mosiacism, Turner's syndrome
    - Drugs taken in utero including DES, danazol, aminoglutethimide, etc.
  - Environmental chemicals
    - Accidental high dose PCB and PCDF exposures in food

In my opinion, the conclusion that studies in rodents on the reproductive effects of phthalates is consistent with EPA risk assessment guidelines that state "For assessment of risk to the human reproductive systems, the most appropriate data are those derived from human studies having adequate study design and power. In the absence of adequate human data, our understanding of the mechanisms controlling reproduction supports the use of data from experimental animal studies to estimate the risk of reproductive effects in humans." These guidelines specifically discuss the use of animal models for assessing reproductive toxicity (http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=2838). They include a default list of assumptions that are listed in the following table.

Table. Default assumptions in reproductive toxicity risk assessment

1. An agent that produces an adverse reproductive effect in experimental animals is assumed to pose a potential threat to humans.
2. Effects of xenobiotics on male and female reproductive processes are assumed generally to be similar unless demonstrated otherwise. For developmental outcomes, the specific effects in humans are not necessarily the same as those seen in the experimental species.
3. In the absence of information to determine the most appropriate experimental species, data from the most sensitive species should be used.
4. In the absence of information to the contrary, an agent that affects reproductive function in one sex is assumed to adversely affect reproductive function in the other sex.
5. A nonlinear dose-response curve is assumed for reproductive toxicity.

Questions from the Honorable Joe Barton

Q1. Please explain how endocrine disruptors (EDCs) have been statutorily banned to date.

As a research biologist in the EPA, it is my understanding that the program offices that regulate chemicals do not specifically ban or regulate chemicals because they display endocrine activity, rather, the chemicals are regulated on their ability to produce adverse effects. Some EDCs have been regulated by the EPA and some of the adverse effects were caused by disruption of the endocrine system. For example, a permanent reduction in prostate weight, an androgen-dependent tissue in the rat, was used as the adverse effect for the androgen receptor antagonist vinclozolin. At higher dosage levels vinclozolin produces male reproductive tract lesions including hypospadias and undescended testes (http://epa.gov/pesticides/reregistration/REDs/factsheets/2740fact.pdf).

In the European Union, DBP, DEHP and BBP were regulated on the male reproductive tract lesions caused by inhibition of fetal testosterone synthesis and a draft EPA risk assessment being conducted under IRIS has concluded that phthalate-induced reduction in fetal testosterone levels is an adverse effect and is using this endpoint to establish a No Observed Adverse Effect Level (NOAEL) for DBP (draft document available at: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=155707).

Q2. Please explain whether there is unanimity regarding how humans metabolize and discard phthalates with regard to rodents.

This is beyond my area of expertise, so I will only make a few comments on the metabolism and excretion of phthalates. Some phthalate esters are metabolized in the gut by nonspecific esterases to the monoesters (which are the toxic metabolites of some phthalates). There are species differences in the activity of the esterases among species and not all phthalates are metabolized via the same pathways or to the same degree (Kluwe 1982; Peck and Albro 1982; Rhodes *et al.* 1986). Once taken up from the gut, monoesters can circulate, as such, or be metabolized and excreted, many being primarily excreted in the urine. Each phthalate ester has its own profile of metabolites in the urine and there are some species differences here as well. Considerable work is ongoing in several laboratories, including the CDC in Atlanta and in Europe (see the published papers of Drs Calafat, Hauser, Koch, Angerer, etc, for example) characterizing the metabolic profile of different phthalate esters in humans.

While there are some species differences in metabolism and excretion of the phthalates, the critical point is that biomonitoring data show that some humans are exposed to some of the active phthalate metabolites. For example, MBP and MEHP, metabolites of DBP and DEHP, respectively, were present in the amniotic fluid of pregnant women (Silva *et al.* 2004) and newborn cord blood(Latini *et al.* 2003), in some cases at high concentrations. Furthermore, the highest levels of monobutyl phthalate found in human amniotic fluid were only about 5 fold lower than those seen in rats exposed to a dosage level that results in adverse effects in male rat offspring (Calafat *et al.* 2006a; Mylchreest *et al.* 1999). In addition, Hauser et al (Hauser *et al.* 2004) reported that the concentration of monobutyl phthalate, a DBP metabolite, in an individual's urine sample was 16,868 ng/ml.

This demonstrates that regardless of metabolism, the human fetus is exposed to phthalate metabolites that are reproductive toxicants in rats. In addition, children in neonatal intensive care units using plastic tubing with DEHP also are exposed internally to high levels of MEHP (Sjoberg and Bondesson 1985; Sjoberg *et al.* 1985a; Sjoberg *et al.* 1985b).

Q3. You testified you intend to study additional phthalates and their potential cumulative effects. Please explain based upon your prior research why you believe additional study is necessary?

I believe additional research is needed on the effects of individual phthalates and mixtures for several reasons:

- There are several important phthalates, e.g., DIDP and DNOP that have not yet been studied.
- There are many phthalates for which there is not any information regarding their ability to disrupt fetal male testis function or what their effects are on reproductive tract development and function; some of these are ones used in consumer products (for example di-isobutyl phthalate has been detected in the urine of pregnant women (Adibi *et al.* 2008)).
- DINP has not yet been included in mixture studies and this phthalate, among others, is being used more in toys and other products than it was in the past.
- Additional, unstudied phthalates should be included in mixture studies on male rat reproductive development to examine how they behave.
- It is important to more fully characterize the effects of individual phthalates and mixtures on the development of the reproductive tract of the female rat. Is the mode of action the same for female effects as male effects? Are these effects induced during the same period of rodent sexual differentiation? It should be noted that effects on the female tract cannot be explained by inhibition of testosterone synthesis that is related to effects in the male rat.
- We plan to continue to conduct mixture studies combining phthalates with pesticides and other toxic substances that disrupt male and female rat reproductive development to determine if we can predict how chemicals with diverse modes of action behave in mixtures; this research is important toward the development of approaches to assess risk to combinations of chemicals that operate under similar and different modes of action.

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September 26, 2008

Response to questions from members of the Subcommittee on Commerce, Trade, and Consumer Protection; US House of Representatives

Ted Schettler MD, MPH
Science Director
Science and Environmental Health Network

Questions from the Honorable Bobby L. Rush:

1) Briefly summarize the science on the harmful effects to children of the following phthalates:

DEHP, DBP, BBP

Normal amounts of testosterone are necessary for normal male development in utero and during infancy. After a period of quiescence during childhood, testosterone again plays an important role in the onset of puberty.

Each of these phthalates interferes with normal testosterone synthesis. Considerable animal data show that sufficient exposure to these phthalates can interfere with normal male reproductive tract development. The relevant biological processes in laboratory animals are widely conserved across species so that the animal data are generally thought to be relevant to humans.

Human data in children are limited. One study reported an association between reduced anogenital distance in baby boys and maternal phthalate exposures (Swan et al. Decrease in anogenital distance among male infants with prenatal phthalate exposure. Environ Health Perspect. 2005 Aug;113(8):1056-61.) Another found an association between altered sex hormone ratios in infant baby boys and maternal milk phthalate levels. (Main et al. Human breast milk contamination with phthalates and alterations of endogenous reproductive hormones in infants three months of age. Environ Health Perspect. 2006;114(2):270-276.) Please also see my written testimony.

DINP:

Please see my written testimony. DINP also interferes with normal testosterone production and is dose additive with other phthalates sharing a common mechanism of action. (see above)

DnOP:

Commercial DnOP is often a mixture of phthalates. According to the National Toxicology Program, toxicity information for pure DnOP is extremely limited. In the commercial mixture, some phthalates may have toxic properties as described above but

the composition of the mixture is likely to vary. I am not aware of any human data addressing the effects of DnOP.

DiDP:

Based on laboratory animal testing, DiDP can cause birth defects, decreased survival, and decreased growth after in utero exposure. I am not aware of any human data addressing adverse effects in humans exposed to DiDP.

Do phthalates affect children of different ages differently?

Probably. Those phthalates that interfere with normal testosterone production would be expected to pose most risk during periods of growth and development when normal levels of testosterone are required.

Does recent research on phthalate mixtures change the state of play on the research?

Yes. Phthalates that interfere with testosterone production have been shown to be dose additive with respect to testosterone-dependent endpoints. The National Academy of Sciences has nearly completed a study addressing aggregate exposures to phthalates for risk assessment purposes, and that study should be available soon.

What are the current uses of individual phthalates in various children's products?

I do not have any direct information addressing this. Unfortunately, manufacturers are under no obligation to inform the public with respect to the materials they use in children's products.

What replacements are available?

Two approaches are possible: 1) Manufacture the product out of a material that does not require the addition of any plasticizer. 2) Use a non-phthalate plasticizer if one is required. Many children's products are available made of materials that do not contain any plasticizer at all. With respect to option two, the appropriate alternative plasticizer would depend on the particular application.

Lack of safety data for alternatives is a poor excuse for continuing to use problematic chemicals in consumer products. Why should a status quo that poses risks be protected by ignorance? Why is it that we do not have requirements for safety testing of all chemicals used in consumer products?

Some have indicated that phthalate research experiments involving rodents may be less relevant than research involving primates. What is your perspective on this issue?

Species differences in pharmacokinetics of phthalates are important to consider. This also means that it is important to consider differences in the kinetics of phthalates in humans

and non-human primates. For example, Koch et al showed that human internal exposures after a single dose of DEHP may be considerably higher than the same dose in marmosets. (Koch H. et al. New metabolites of di(2-ethylhexyl)phthalate (DEHP) in human urine and serum after single oral doses of deuterium-labeled DEHP. Arch Toxicol. 2005 79(7):367-76.)

With respect to the endpoints of toxicity, based on what we know about mechanisms of action, rodent research is highly relevant for predicting impacts in people. Please see the National Toxicology Program's discussion of this topic.

Research involving primates is very useful, but not all primates are the same. For example, marmosets, which have been used in some phthalate research, have a hormonal system that differs in fundamental ways from humans. (Li, et al. Review on testicular development, structure, function, and regulation in common marmoset. Birth Defects Res B Dev Reprod Toxicol. 2005 74(5):450-469.) As a result, it is important to critically review which data are likely to be applicable to humans and which are not.

Secondly, in order to study impacts of phthalates in developing organisms, exposures must occur during windows of vulnerability. To my knowledge, virtually all primate research with phthalates has been carried out in adult animals, in animals post-weaning, or in animals that have already entered puberty. I am not aware of studies examining impacts of phthalates in primates in utero or immediately after birth.

Questions from the Honorable Joe Barton:

Describe the normal route of human exposure to phthalates, the sources of human exposure, and in what quantities humans are exposed.

Please see attached paper. (Schettler T. Human exposure to phthalates via consumer products. Int J Androl. 2006 29(1):134-9; discussion 181-5. Review.)

For quantities, please see monographs of the CERHR of the National Toxicology Program and NHANES data from the Center for Disease Control and Prevention.

How are some people exposed to higher levels than others?

Phthalate exposures come from many sources including the diet, consumer products, and the ambient environment. Individual variability in those pathways is likely to explain inter-individual differences in exposure levels.

Testimony regarding men being treated in an infertility clinic having reduced sperm counts or sperm quality:

The study I referred to in my testimony included only men from an infertility clinic. The data were controlled for age, smoking, and abstinence time. In order for other

environmental or genetic factors to bias (distort) the association of phthalates and semen quality, those other factors would need to be associated with BOTH phthalate levels AND semen quality. It is highly unlikely that genetic makeup would be associated with both phthalate levels and semen quality. In addition studies show that phthalate exposures have low correlation with other environmental chemicals such as PCBs and pesticides. Although it is theoretically possible that some other environmental or health factor could correlate with both phthalate levels and semen quality, it is highly unlikely. Consequently, there is little concern that the results of this study are actually attributable to an unidentified confounder.

Please describe any plastics that you consider safe:

1) In order to conclude that something is "safe", both hazard and exposure data are necessary. Any plastic that does not have hazardous properties or that does not result in an internalized exposure to a chemical with hazardous properties (under any circumstances, during its life cycle) does not pose a risk. Any plastic fulfilling those criteria is "safe."
2) That said, "safety" is a relative concept inasmuch as some materials pose less risk than others. And the context in which materials are used also matters. As I elaborated in my written and oral testimony, people are not exposed to single chemicals from single sources. Evaluating risks associated with exposures to chemicals from any plastic must be considered in real-world circumstances of multiple exposures from multiple sources.
3) Proving that something is safe can be difficult, and many point out that it is logically impossible to prove that something adverse will never happen. I agree, but evaluating safety is not impossible. We sometimes hear that alternatives for certain chemicals used in products have not been evaluated for their safety and may pose a greater risk than what they are intended to replace. When consumer product manufacturers can replace a tested chemical that raises health concerns with a chemical that has not been evaluated for safety, the inadequacy of our current regulatory regime becomes obvious. It is a regime that rewards ignorance, and it needs to be replaced with a system that requires safety testing data.

Questions from the Honorable Diana DeGette:

Are statutory standards pursuant to which the CPSC is authorized to issue consumer protection regulations adequate to protect consumers and public health?

I cannot comment on what the standards permit. My concerns with the CPSC are two-fold. First, when they do evaluate the safety of a product, they do not have a routine practice of assessing risk in a real-world context of multiple exposures from multiple sources. If, for example, a product contains DINP, they evaluate exposures and attendant risks as if that product were the only source of DINP for an individual. We know that not to be true. Moreover, CPSC does not consider aggregate exposures to other phthalates

with common mechanisms of toxicity. The same critique pertains to lead or other hazardous materials.

Secondly, CPSC either does not have the resources or the inclination to routinely monitor the safety of consumer products in a systematic way. As a result, consumer activist groups have turned out to be a fall-back source of information about hazardous materials in consumer products. Systematic monitoring of consumer products for chemical hazards as well as physical hazards should be routine.

I cannot compare CPSC standards to those of other countries. With respect to other agencies, however, labeling requirements would be helpful. Active ingredients of pesticides must be listed on containers so that consumers will know what is present. (EPA) Pharmaceuticals must be labeled. (FDA) Food must be labeled. (FDA) Cosmetics are supposed to be labeled with their ingredients. (FDA) But other consumer products have no labeling requirements. Without required safety testing or labeling of ingredients, buyers must simply beware. They are on their own.

From: Ted Schettler [tschettler@igc.org]
Sent: Friday, August 22, 2008 2:45 PM
To: Baron, Valerie
Subject: Re: Questions for the Record

Attachments: human exposure to phthalates, ija.pdf

Valerie,

I covered many of these questions in my written and oral testimony.

I am attaching a copy of a paper that I published addressing exposure to phthalates. It contains the answers to some of the questions.

A more detailed response to these open ended questions is not possible in this short time frame in mid-August.

Best regards,

Ted Schettler

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Human exposure to phthalates via consumer products

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Keywords:
butyl benzyl phthalate, consumer products, dibutyl phthalate, di-(2-ethylhexyl) phthalate, exposure, phthalate

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Summary

Phthalate exposures in the general population and in subpopulations are ubiquitous and widely variable. Many consumer products contain specific members of this family of chemicals, including building materials, household furnishings, clothing, cosmetics, pharmaceuticals, nutritional supplements, medical devices, dentures, children's toys, glow sticks, modelling clay, food packaging, automobiles, lubricants, waxes, cleaning materials and insecticides. Consumer products containing phthalates can result in human exposures through direct contact and use, indirectly through leaching into other products, or general environmental contamination. Historically, the diet has been considered the major source of phthalate exposure in the general population, but all sources, pathways, and their relative contributions to human exposures are not well understood. Medical devices containing di-(2-ethylhexyl) phthalate are a source of significant exposure in a susceptible subpopulation of individuals. Cosmetics, personal care products, pharmaceuticals, nutritional supplements, herbal remedies and insecticides, may result in significant but poorly quantified human exposures to dibutyl phthalate, diethyl phthalate, or dimethyl phthalate. Oven baking of polymer clays may cause short-term, high-level inhalation exposures to higher molecular weight phthalates.

Introduction

Phthalates are a family of chemicals used in many consumer products, including building materials, household furnishings, clothing, cosmetics, personal care products, pharmaceuticals, nutritional supplements, herbal remedies, medical devices, dentures, children's toys, glow sticks, modelling clay, food packaging, automobiles, lubricants, waxes, cleaning materials and insecticides. Phthalates provide plasticity to otherwise rigid materials such as polyvinyl chloride and other polymers. They also lubricate, act as solvents, and otherwise impart favourable characteristics to products.

Annually, more than three million metric tonnes of phthalates are produced globally (Bizzari *et al.*, 2000). Uses of the various phthalates depend in part on their molecular weight (MW). Higher MW di-(2-ethylhexyl) phthalate (DEHP), di-isononyl phthalate (DiNP), and di-isodecyl phthalate (DiDP) are the phthalates produced in highest volume for use in construction material, clothing and furnishings. By far, their largest application is to impart flexibility to polyvinyl chloride plastic (PVC). Relatively low MW phthalates such as diethyl phthalate (DEP), dimethyl phthalate (DMP) and dibutyl phthalate (DBP) tend to be used as solvents and in adhesives, waxes, inks, cosmetics, insecticides and pharmaceuticals. Single applications may also use mixtures of phthalates.

Because of their widespread use, all populations of people, domestic animals, and wildlife regularly encounter opportunities for exposure to phthalates. This paper reviews data regarding various sources and pathways of human exposure to phthalates from consumer products. Data gaps are numerous, which makes it difficult to explain fully the relative contributions of various sources of phthalates to exposures reported in the general population (CDC, 2005).

Routes of exposure to phthalates

The physicochemical characteristics of phthalates vary with the chemical structure and may include a vapour phase, although vapour pressures are generally low. Phthalates are generally lipophilic, which influences their leaching and environmental partitioning characteristics.

Ingestion, inhalation, intravenous injection and skin absorption are potential pathways of exposure. Human

exposure to phthalates can occur as a result of direct contact or use of a product containing phthalates, through the leaching of phthalates from one product into another, as may occur with food packaging (Aurela *et al.*, 1999) or intravenous fluids, or by general contamination of the ambient environment.

Ingestion

Phthalate ingestion may occur via food, including enteral nutritional formulas, pharmaceuticals, nutritional supplements, sucking children's toys and other mouthing objects.

Food

Dietary intake from contaminated food is likely to be the largest single source of phthalate exposure in the general population. Phthalate levels in food, however, are widely variable, and data are often old and may not reflect current exposure levels. Estimates include: DBP maximal daily intake 0.48 μg/kg/day (MAFF, 1996), DEHP 4.9–18 μg/kg/day (Meek & Chan, 1994), butyl benzyl phthalate (BBP) 0.11–0.29 μg/kg/day (MAFF, 1996).

Medical devices

Medical devices made of polyvinyl chloride softened with DEHP for administering i.v. solutions, blood, nutritional formulas and respiratory gases leach varying amounts of the phthalate. Solutions containing lipids facilitate leaching. Enteral formula containing lipid emulsion stored in a polyvinylchloride (PVC)/DEHP bag and delivered through PVC/DEHP tubing is estimated to result in a maximal daily DEHP exposure of about 9.5 mg/day, or 0.14 mg/kg/day in adults, whereas neonatal infants may be exposed to 2.5 mg/kg/day via this pathway (FDA, 2001).

Pharmaceuticals, herbal preparations, nutritional supplements

Pharmaceutical preparations are often coated with a polymer that influences the timing and location of drug delivery in the gastrointestinal tract. Eudragit is an ammonia methacrylate copolymer coating that remains intact in low gastric pH but breaks down in the higher pH of the lower intestine (Chourasia *et al.*, 2003). Various plasticizers, including DBP and DEP, may be added to Eudragit to influence drug delivery in the intestine. An internet search of the US Patent Office data base (http://www.patentstorm.us/) produces many examples of pharmaceutical products that may have phthalate plasticizers, including DBP and DEP, in their coatings. Among them are commonly used antibiotics, antihistamines and laxatives. Patented herbal preparations and nutritional supplements, including those intended for use during pregnancy, may also incorporate phthalates in the formulation.

A case report identified high levels (16 868 ng/mL) of the monoester metabolite of DBP in the urine of a man who had taken Asacol for ulcerative colitis (Hauser *et al.*, 2004). This concentration is two orders of magnitude higher than the 95th percentile in the US population-based NHANES report. Commonly used pharmaceuticals, herbal preparations and nutritional supplements may be important uninvestigated sources of phthalate exposure in the general population.

Toys

Polymer toys softened with phthalates are a source of potential oral exposure in children. The European Union has temporarily banned marketing of all children's toys and child-care articles containing DEHP, DBP, and BBP as well as toys containing DiNP, di-*n*-octyl phthalate (DnOP) and DiDP intended for children <3 years old. Primarily DiNP is used in toys in the US. Estimates of mean DINP exposure resulting from children's mouthing activities range from 5.7 to 44 μg/kg/day depending on assumptions and statistical techniques. The 99th percentile estimate ranges from 40 to 173 μg/kg/day (Kavlock *et al.*, 2002a).

Inhalation

Medical devices

DEHP may be transferred into respiratory gases passing through PVC tubing, although quantification of exposure has rarely been attempted. Hill estimates exposure to DEHP via respiratory therapy at 28.4–94.6 μg/day, based on direct measurement under experimental conditions (Hill, 1997).

Baking modelling clay

Polymer modelling clay is formed and then cured by baking in an oven. A complex mixture of phthalates imparts a soft consistency to the material at room temperature. Ten samples of Sculpey and Fimo clay contained total phthalate levels ranging from 3.5% to 14% by weight. Individual phthalates identified included DnOP, di-*n*-hexyl phthalate, BBP, DEHP and terephthalic acid (Maas *et al.*, 2004). Air concentrations of the phthalates after baking were reported for BBP (32–2667 μg/m^3), and DnOP (ND-6670 μg/m^3). DEHP and/or chemically similar analogues were detected at 6.05–4993 μg/m^3. For short-term exposures, the US EPA recommends using a mean of 1.0 m^3/h as an estimate of respiratory volume in children <18 years of age. For a 1-h exposure period, this would result in maximal inhalation exposures for BBP,

DnOP and DEHP or similar compounds of 2667, 6670 and 4993 μg respectively.

House dust and indoor air

Indoor air and dust contains phthalates that leach from building products, household furnishings, toys, clothing, accessories (e.g. children's PVC backpacks), and inside automobiles from plasticized components. General environmental contamination with phthalates contributes to some unspecified degree to food, water and indoor dust levels.

Rudel *et al.* (2001) reported total phthalate concentrations in dust from one office and five homes ranging from 0.3 to 524 μg/g dust. Phthalate air concentrations from samples from other locations ranged from 0.005 to 28 μg/m^3.

Becker *et al.* (2004) reported levels of DEHP in the house dust of 254 children whose urinary metabolites of DEHP were also measured. The mean house dust level was 508 μg DEHP/gm dust, with no correlation between house dust levels and urinary levels of DEHP metabolites in the sample, suggesting that house dust is not a major contributor to total DEHP exposure. Another study of phthalate exposure via inhalation using personal air monitors also found no significant correlation between DEHP air levels and the urinary monoester metabolite, mono ethylhexyl phthalate (MEHP). However, a significant correlation for DEP, DBP and BBP was identified, suggesting that inhalation may be an important pathway of exposure for lower molecular weight phthalates (Adibi *et al.*, 2003).

Oie *et al.* (1997) reported a mean of 960 μg total phthalates/g dust in 38 homes in Norway (range 130–2920 μg/g dust). DEHP was the largest contributor (mean 640 μg/g dust; range 100–1610). They estimated mean adult inhalation exposure to DEHP from this source to be 0.76 μg/day. Ingestion of dust contaminated at 640 μg DEHP/g dust ×100 mg dust ingestion/day would yield a dose of 64 μg/day.

Otake *et al.* (2004) analysed phthalate levels in indoor air of 27 houses in Tokyo. They reported median concentrations of DEP, DBP, BBP, dicyclohexyl phthalate, and DEHP of 0.10, 0.39, 0.01, 0.07, and 0.11 μg/m^3 respectively. For an adult breathing 20 m^3/day, these would result in inhalation exposures of 2, 78, 0.2, 1.4 and 22 μg/day respectively. Inhalation of contaminated dust will result in larger inhalation exposures.

Intravenous

A variety of medical devices made of PVC plasticized with DEHP are used to deliver medical care. Bags and/or tubing deliver intravenous fluids, nutritional formulas, blood and are used for extracorporeal membrane oxygenation and dialysis. Leaching of DEHP from the device varies with lipid content, temperature, storage time and agitation (FDA, 2001). Table 1 shows the estimates of parenteral exposure to DEHP that may result from various procedures. Individual studies show some variability in exposure levels, depending on specific conditions and equipment choices. For example, DEHP exposure from extracorporeal membrane oxygenation (ECMO) can be reduced considerably by using heparinized PVC/DEHP tubing (Karle *et al.*, 1997).

Table 1 Intravenous exposures to DEHP from select medical procedures using medical devices made of PVC containing DEHP (modified from FDA, 2001)

	Adult	Neonate
	DEHP dose (mg/kg/day)	
Crystalloid i.v. solutions	0.005	0.03
Total parenteral nutrition		
Without added lipid	0.03	0.03
With added lipid	0.13	2.5
Blood transfusion		
Trauma patient	8.5	
Transfusion/ECMO	3.0	
Exchange transfusion		22.6
Replacement transfusion		0.3
Coronary artery bypass graft	1	
ECMO		14

Calafat *et al.* (2004) measured DEHP metabolites in the urine of six premature infants receiving intensive medical therapy, including i.v. infusions, and reported that the median level of the metabolite MEHP (129 ng/mL) in these children was significantly higher than the median in the general population NHANES study (2.7 ng/mL). Green *et al.* (2005) measured DEHP metabolites in the urine of 54 newborn children in two neonatal intensive care units. This study documented higher levels of urinary metabolites of DEHP with increasing intensity of care and more frequent use of DEHP-containing devices. Mean urinary MEHP levels in low, medium and high intensity care infants were 9.3, 41, 139 ng/mL respectively.

Skin absorption

Skin may come into direct contact with phthalate-containing clothing, cosmetics, sunscreens, insecticides, other personal care products, modelling clay, toys, yoga pads, waxes, cleaning products and denture material (Munksgaard, 2004).

In general, transdermal absorption depends on chemical concentration, chemical structure, water solubility, octanol : water partition coefficient between the

formulation vehicle and stratum corneum, the formulation vehicle, and the anatomic area of application (US EPA, 1992). Skin absorption of chemicals from the face, axilla and scrotum, for example, may be up to 10-fold higher than the arm.

Studies using rodent skin show that absorption of phthalates is generally slow. An in vitro comparison demonstrated that human skin is less permeable to phthalates than is rat skin, although studies of human skin are few (Scott *et al.*, 1987; Elsisi *et al.*, 1989). An in vivo study of DBP absorption through human upper arm skin showed a maximum flux of 10 $\mu g/cm^2/h$ (mean = 3.8) when applied as a saturated solution of DBP in propylene glycol (Hagedorn-Leweke & Lippold, 1995). The authors concluded that the octanol : vehicle partition coefficient is the largest determinant of skin absorption.

Dimethyl phthalate and DBP have been used topically as insect repellants (Ware & Whitacre, 2004). DBP, DEP, DMP and DnOP are currently on the US EPA's list of 'potentially toxic inerts', and may be used along with other ingredients in insecticides or repellants, causing dermal or inhalation exposures.

Quantification of internal exposures to phthalates from commercially available products that are applied to the skin is not generally available.

Data gaps

Significant data gaps make it difficult to identify with certainty the various sources, exposure pathways and their relative contributions to observed human phthalate levels in the general population. Dietary phthalate data are outdated. Exposures from pharmaceutical products, herbal remedies and nutritional supplements are generally not quantified. The relative contribution of transdermal and inhalation pathways from cosmetics, other personal care products and insecticides is unknown. Foetal exposures to DEHP from medical care or other sources during pregnancy have not been quantified, although DEHP and its metabolites are known to cross the placenta (Latini *et al.*, 2004).

The presence of phthalates in consumer products may not be apparent, even in cosmetics that are subject to strict labelling requirements. One study analysed 72 cosmetics and personal care products purchased directly from stores (http://www.nottoopretty.org/). Phthalates were not identified on any of the labels. Phthalates were present in 52 of the products, including deodorants, fragrances, hair gels, mousses, hair sprays, and hand and body lotions. Nail polish may also contain high concentrations of unlabelled DBP.

Koch et al. have recently demonstrated that DEHP is metabolized into at least five metabolites, including MEHP, 5OH-MEHP, 5oxo-MEHP, mono(2-ethyl-5-carboxypentyl)phthalate, and mono[2-(carboxymethyl)hexyl]phthalate (Koch, 2005). Earlier attempts to quantify total DEHP exposure that relied on measuring fewer metabolites undoubtedly resulted in underestimates, as the newly identified carboxy-metabolites comprise approximately 22% of the molar concentration of all metabolites. However, the pathway of exposure to DEHP and individual and age-related variability in metabolic pathways are likely to influence metabolite profiles (Schmid & Schlatter, 1985; Anderson *et al.*, 2001; Barr *et al.*, 2003; David, 2003; Koch *et al.*, 2003, 2004).

Conclusions

Consumer products containing phthalates can result in human exposures through direct contact and use, by leaching into other products, or via general environmental contamination. Phthalate exposures in the general population and in subpopulations are ubiquitous and sources are widely variable.

In the general population, the diet is generally considered the major pathway of exposure but all sources, pathways, and their relative contributions to measured body burdens of phthalates are not well understood. Phthalates may be present but unidentified in many consumer products, including cosmetics, personal care products, home furnishings, pharmaceuticals, nutritional supplements and insecticides. In some instances, these may be important but unquantified sources of exposure. Oven baking of polymer clays may cause short-term, high-level inhalation exposures. Medical devices made of PVC containing DEHP are an important source of exposure to this reproductive and developmental toxicant in susceptible populations.

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Discussion

Dr NE Skakkebæk (Copenhagen, Denmark)
What proportion of the daily intake of phthalates is derived from food and drink?

Dr T Schettler (Newburyport, MA, USA)
Food has traditionally been considered to be the major single source of exposure to DEHP and other phthalates. However, new data on metabolites of phthalates in humans have revealed, in some cases, higher exposures than previously estimated in the general population. For some phthalates non-food sources may be more important, but the relative contributions from each source are still not well understood.

Dr D de Kretser (Melbourne, Australia)
Given the considerable time that the postulate that phtalates may adversely affect reproduction, it is surprising that there is no evidence about a mechanism of action. Given their structure, it should be possible to radioactively label these compounds and ascertain whether they bind to target tissues. Could they, for instance, bind to putative orphan steroid receptors that lack a defined ligand?

Dr H Leffers (Copenhagen, Denmark)
I fully agree that it is crucial to elucidate the mode of action of phthalates in the testis. However, a few studies have looked at the distribution of DEHP and metabolites (for example *Ono et al.*, *The Journal of Toxicological Sciences*, 2004; 29: 113). Also, reports on interactions between the toxic metabolites (the monophthalates) and different receptor systems, incl. PPAR receptors, are beginning to emerge (for example *Hurst & Waxman*, *Toxicological Sciences*, 2003; 74: 297). Nevertheless, much more knowledge is clearly needed to understand the apparently very restricted effects on Leydig cells, and thus their effects on male reproduction.

99 Newport Landing Drive
Novato, California 94949
August 20, 2008

Representative John D. Dingell
U.S. House of Representatives
c/o Ms. Valerie Baron
House Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, D.C. 20515-6115

Dear Chairman Dingell,

I am writing in reply to your letter of August 8, 2008 and the questions submitted by Vice Chair DeGette concerning current Federal standards and procedures and how those compare to standards and procedures utilized in the European Union.

Attached please find the response to Vice Chair DeGette's inquiry. I trust this information will help reduce the mortality, morbidity and health care costs associated with current US policy. I have provided a brief account of an on-going US and EU cooperative program that includes representative stakeholders from academia, the public and private sectors that has worked very well and that could be applied to address the concerns raised by Vice Chair DeGette.

Should your office require additional references, documentation or supporting materials, I can be contacted at the above address.

Sincerely yours,

Calvin C. Willhite, Ph.D.

United States House of Representatives
August 20, 2008

PUBLIC HEALTH AND THE HOUSE COMMITTEE ON ENERGY AND COMMERCE

Calvin C. Willhite, Ph.D.
99 Newport Landing Drive
Novato, California 94949

On June 10, 2008 the House Committee on Energy and Commerce held a public hearing, "Safety of Phthalates and Bisphenol A in Everyday Consumer Products". Subsequent to that hearing, Vice Chair DeGette posed three questions relating to current Federal statutory standards, how those standards compare to those promulgated by the European Union and other foreign entities and what actions could be taken by Congress to improve public health in our country.

Background

A fundamental tenant of toxicology is that all substances are poisons; that is, the exposure (or dose) makes the poison (Gallo, 1996). There is no division in toxicology between exposure to a chemical found in consumer products (e.g., polyurethane foam) or exposure to that very same chemical (e.g., toluene diisocyanate or TDI) used in the manufacture of those consumer products. Taking relative exposure into account, it stands to follow that we gain the greatest health benefit when we control high exposures to very toxic substances.

United States House of Representatives
August 20, 2008

What is the Problem?

In the Bhopal (India) disaster of 1984, 2000 residents were killed and 20,000 were left blind and/or suffered permanent damage to their lungs after the industrial release of a gas called methyl isocyanate. There are at least 400 such materials and they are called extremely hazardous substances or EHSs (National Research Council, 2001). Other than accidental or intentional release of EHSs like methyl isocyanate, the highest exposures are experienced by people who handle these substances each and every day as part of their job.

In 1971, the Department of Labor (DOL) adopted workplace exposure limits (known as Permissible Exposure Limits or PELs) codified as 29 CFR 1910.1000 and these were accompanied by Tables Z-1, Z-2 and Z-3. The PELs are enforceable limits that specify the maximum concentrations of a chemical in workplace air and the maximum length of time to which a person may be exposed to that level. The 1971 PELs were based primarily on a list of consensus guidelines known as the Threshold Limit Values (TLVs) developed over many years by volunteers of the American Conference of Governmental Industrial Hygienists, a not-for-profit organization chartered in Ohio. Those limits were based on knowledge gained from research conducted in the 1950s and 1960s.

On January 19, 1989, the DOL published a Final Rule at 54 FR 2332-2983 that updated the PELs for 212 toxic air contaminants and established limits for 164 toxic substances that had not been regulated previously. At that time, DOL concluded that action would "result in a reduction of 700 deaths, 55,000 illnesses and over 23,300 lost-

workday illnesses annually." On July 10, 1992, the Eleventh Circuit Court of Appeals vacated the 1989 rule as a result of its decision in *American Federation of Labor and Congress of Industrial Organization et al. v. Occupational Safety and Health Administration, Department of Labor* (965 F.2d 962 11th Cir. 1992). The Court's action forced the DOL (1993) to return to the earlier PELs. At that time, OSHA continued "to believe that many of the old limits which it will now be enforcing are out of date (they predate 1968) and are not sufficiently protective of employee health based on current scientific information and expert recommendation. In addition, many of the substances for which OSHA has no PELs present serious health hazards to employees." Those old inadequate limits are the limits that are used to this very day.

Since the Eleventh Circuit Court's vacation of the revised PELs in 1992, OSHA made some effort to address the problem. In 1996, the DOL proposed updating 20 of the PELs (carbon disulfide, carbon monoxide, chloroform, dimethyl sulfate, epichlorohydrin, ethylene dichloride, glutaraldehyde, n-hexane, 2-hexanone, hydrazine, hydrogen sulfide, manganese, mercury, nitrogen dioxide, perchloroethylene, sulfur dioxide, toluene, toluene diisocyanate, trimellitic anhydride and vinyl bromide). In 2000, the Agency reduced that number to four (carbon disulfide, glutaraldehyde, hydrazine and trimellitic anhydride). As of 2008, the only updates to the PELs were for two chemicals, including that in 2006 for the known human carcinogen hexavalent chromium - as a result of an order by the U.S. Court of Appeals for the Third Circuit. Even in that case, the federal standard only requires employers to "implement feasible engineering controls by May 31, 2010". At this rate, it is impossible the Agency will ever address the 700 existing

chemicals or develop PELs for chemicals like bisphenol A that have never been assigned a PEL.

What Do Other Countries Do?

Countries within the European Union do not all adopt and follow identical standards in each and every situation; in the case of occupational exposure limits, they function as independent states. Details of the procedures used by all EU member nations as well as those used by Australia, New Zealand, Canada, Japan and even Estonia can be found at the web site for the European Agency for Safety and Health

[http: // osha.europa.eu/en/good_practices /topics/ dangerous _ substances/oel/nonmembers.stm/ members.stm].

Five countries are particularly active in this aspect: France, Germany, The Netherlands, Sweden and the United Kingdom. For sake of brevity, only Germany and Sweden are described here.

The Germans develop two kinds of values, the health-based MAKs (Maximale Arbeitsplatzkonzentrationen) and the TRKs (Technische Richtkonzentrationen). The MAKs are maximum limits that are derived using methods very similar to the American TLVs and both the MAKs and TLVs are intended for an 8 hour workday. The TRKs are the maximum concentrations that can be achieved using the best available technology. We have no values similar to TRKs in the United States. The Swedes also promulgate maximum limits developed by the Arbeitslivsinstitutet; execution of the chemical control ordinance is the responsibility of the Arbetsmiljoinspektionen. An example of a Swedish

limit is that for TDI (National Institute for Working Life, 2001) where the Swedish Work Environment Authority (2006) promulgated an 8 hour limit of 0.002 parts per million – a value 10 times less than the current U.S. federal PEL (DOL, 1993). The revised Swedish limit is based on the recognition that TDI is a potent respiratory tract sensitizer that induces asthma to the point that affected people relocate, seek transfers or are disabled.

What Can Congress Do?

It is not clear whether failure of the DOL to revise the PELs over the past 16 years is the result of neglect, is the result of the sheer size of the effort required, is the result of legal obstacles or whether it is intentional. Based on the 1989 DOL annual estimates, the 16 years since the Eleventh Circuit Court's ruling vacating the PELs brought us a total of 11,200 unnecessary deaths, 880,000 avoidable cases of occupational disease and at least 372,800 lost work days due to occupational illness as a result of excessive exposure to toxic chemicals. Is the Nation prepared to continue to absorb this loss in productivity and are we prepared to continue to endure this burden and the medical costs that accompany mortality and morbidity of this magnitude?

The House Subcommittee on Workforce Protection held hearings on "generic rulemaking" so that the hundreds of outdated PELs could be revised and dozens of previously unregulated chemicals (e.g., bisphenol A) could be addressed, but as of this date no progress has apparently been made. The House Committee on Education and Labor took action with HR5522 requiring OSHA to issue standards to control

combustible dust, but this action occurred only after industrial explosions and workplace fatalities.

It has been at least a decade since the problem of significant health risk associated with the current 29 CFR 1910.1000 became obvious - even to OSHA. Given the Executive Branch record taken together with the high legal bar set by the Eleventh Circuit Court, the problem of the antiquated and now largely irrelevant federal PELs can only be addressed by Congress. Objections have been raised to legislation of revised PELs for fear that amendments would either dilute or otherwise corrupt the effort. Legislation of PELs has the fundamental disadvantage that addition of new substances or future revisions to PELs enacted in that manner would require acts of Congress.

There are at least three avenues to address the situation that have not been explored. First, Congress could transfer the responsibility for PEL development and promulgation from DOL to EPA and continue the enforcement responsibility with DOL. Second, Congress could change the rulemaking standard in order that DOL could proceed with promulgation of revised PELs. Third, Congress could establish an independent effort similar to the Acute Exposure Guideline Limit (AEGL) program sponsored by the U.S. with EU participation by The Netherlands, Sweden, Germany, the United Kingdom and France (National Research Council, 2001). Details of that program are available at the National Academy web site (nas.edu) where member countries reach consensus on ambient air concentrations and limits on duration of exposure. The goal of the consensus AEGL program is a uniform approach such that the limits on EHSs in ambient air that apply to the Port of Long Beach are no different from limits that apply to the Ports of Rotterdam or Stockholm or any other similar facility across the globe. The AEGLs have

an enviable record with the production of limits for some 300 chemicals for three different levels of concern (nondisabling, disabling, lethal) and five different durations of exposure (10 minutes to 8 hours).

Given the magnitude of international trade, the global economy and the uniform desire to assure the public health is protected to the extent possible, there is no reason that occupational exposure limits should not also be consistent between the EU members, our other trading partners and the United States.

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August 22, 2008

U.S. House of Representatives
Committee on Energy and Commerce
Subcommittee on Commerce, Trade and Consumer Products
2125 Rayburn House office Building
Washington DC 20515-6115

Att: Ms. Valerie Baron

Dear Ms. Baron:

Attached are my responses to the follow-up questions that members of the Subcommittee on Commerce, Trade and Consumer Products asked me regarding my testimony before the Subcommittee on the "Safety of Phthalates and Bisphenol-A in Everyday Consumer Products" on June 10, 2008.

Please let me know if you need any additional information.

I thank you for inviting me to participate in this process and I look forward to following the progress of the Subcommittee on this matter.

Sincerely,

Stephen U. Lester
Science Director

Follow-up questions submitted by Committee on Energy and Commerce Subcommittee on Commerce, Trade and Consumer Products

Responses prepared by

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August 22, 2008

Questions submitted by the Honorable Bobby L. Rush

1. Please briefly summarize the state of the science on the harmful effects to children of the following individual phthalates:
   - DEHP, DBP, BBP?
   - DINP (also DnOP and DIDP)?
   - Other commercial phthalates not named?

Response: My testimony did not address the science of the harmful effects of phthalates on children. I would defer this question to other members of the panel who did testify on this matter including Dr. Earl Gray, Dr. Ted Schettler, and Dr. John Bucher. However, I will briefly address this question.

An excellent summary source for the adverse effects of phthalates in general and to children is the toxicity profiles prepared by the U.S. Department of Health & Human Services (HHS) Agency for Toxic Substances and Disease Registry (ATSDR). They have prepared profiles on Di (2-ethylhexyl) phthalate (DEHP), Diethyl phthalate (DEP), Di-N-butyl phthalate (DBP), and Di- N-octyl phthalate (DnOP). These reports are available on the ATSDR website at http://www.atsdr.cdc.gov/toxpro2.html#bookmark05.

There are many peer-reviewed scientific studies that have linked phthalate exposure to serious health hazards in children including reduced testosterone levels[1 2 3], lowered sperm counts[4 5 6 7], early puberty in girls[8], genital defects in baby boys[9 10 11 12 13] and respiratory disorders[14 15]. Moreover, several studies in humans have shown some of these toxic effects at levels similar to what the average American is currently exposed to[16 17].

Many of these studies have been replicated in controlled laboratory settings conducted by government agencies and independent research scientists. Male genital abnormalities[18 19 20 21 22] and female sexual abnormalities[23 24 25] resulting from phthalate exposure have been demonstrated in animal studies. Such studies are widely recognized to bear direct relevance to the health risks posed to humans, based on the similarities in each endocrine system and

other physiology of the studied animals and humans. The hormonal signals that guide development of the reproductive tract are the same in rodents as they are in humans.

2. Do phthalates affect children of different ages differently?

Response: My testimony did not address the science of the harmful effects of phthalates on children. I would defer this question to other members of the panel who did address the toxicity of phthalates including Dr. Earl Gray, Dr. Ted Schettler, and Dr. John Bucher. In addition to my response to Question Number 1 above, I will briefly address this question.

Children, especially infants, are especially vulnerable to the toxic effects caused by exposure to chemicals because they are rapidly growing and developing. A report of the International Forum on Chemical Safety of the World Health Organization[26] categorized the elements of a child's changing sensitivity as follows:

- Biology: Vulnerability to toxic exposures during critical periods of ontogenesis, and characteristics of metabolism at various stages of development affecting the fate of xenobiotics inside the human body (age-related toxicokinetics);

- Physiology: Functional features of the developmental stages of the child affecting body burden and internal dose of xenobiotics;

- Behavior: Age-related exposure patterns of the child including physical location in the environment, activity patterns, and behaviors typical of different life stages.

The report goes into significant details about each of these categories including how they overlap and interact.

In addition, evidence is mounting that, when it comes to chemicals and children, it's not just the dose that makes the poison. Timing of exposure is just as important[27 28]. Infants and children are not just smaller adults. They are still developing and are changing almost every day. A small dose of a chemical can have a devastating impact one day whereas a few days or weeks later, the chemical would not have the same effect. This is because their endocrine systems are exquisitely sensitive and are sending signals to the brain and vice versa to direct growth and development. Phthalates interrupt these critical signals and, although the effects may not show up for many years, this interruption can set children on a path for later life diseases such as infertility or cancer of the prostate or breast[29 30].

For infants, the most vulnerable population, exposure to phthalates takes multiple routes: phthalates enter the womb through the umbilical cord or later through mother's breast milk. Exposure can come from dust in the air, from plasticized wall coverings or flooring and from decaying resins in plastic containers. It can also come from sucking on plastic toys. Infants, according to the Intergovernmental Forum on Chemical Safety, an affiliate of the World Health Organization[31], have far less capacity for detoxifying chemicals than do adults, and with toys they face all three points of a "risk triangle": increased vulnerability to a chemical's

toxic effects and plenty of possibilities for exposure through "intimate contact."

3. Does recent research on phthalate mixtures change the state of play on the research?

   Response: This question is not clear. I am uncertain what is meant by "... the state of play on the research." I may be able to address this question if clarified. However, my testimony did not address the state of the research on phthalate mixtures. This is not my area of expertise. I would defer this question to other members of the panel who did testify in general to this matter notably Dr. Earl Gray.

4. As far as you are aware, what are the current uses of the individual phthalates in various children's products?
   - In toys?
   - In products that are intended to be placed in children's mouths (especially pacifiers, rattles, and teethers)?

   Response: Although the CPSC reached a voluntary agreement with industry in the late 1990's to remove phthalates from pacifiers, rattles and teethers, this was strictly a voluntary agreement. Phthalates have been found in teethers since then. In particular, independent studies conducted by the S*an Francisco Chronicle*[32] in 2006 and Environment California[33] in 2005 found phthalates including DEHP, DINP, DNOP, and BBP in children's toys they tested. The Chronicle study tested 18 toys including two teething rings and found DEHP in one of the rings. In the Environment California study, 3 out of 4 of the teethers they tested contained phthalates. They found DBP in two of the teething rings and DEHP in a third teething ring.

   In addition, recent toy testing conducted by the California Department of Toxic Substance Control on behalf of the City of San Francisco found five phthalates —DEHP, DBP, DINP, DNOP and DIDP—in a sample of 31 randomly selected toys currently available on the market today. One or more of these phthalates were found in 19 of the 31 (61%) toys tested[34].

   Another concern is that the presence of phthalates rarely appears on labels of toys sold in the U.S. As a result, parents have no way of knowing if the toys they are giving their kids to play with – and teeth on – have been manufactured with phthalates without sending them to a lab, an expensive and impractical option for parents.

5. To the best of your knowledge, what replacements are available for these phthalates in children's products?
   - What is the state of the science on the safety of any such replacements?
   - Are these alternatives currently available? Are they currently being used?

   Response: Many alternatives are already available and in use as reflected in the experience of toy manufacturers in the European Union (EU) and other countries where these harmful chemicals are banned. Prior to the EU's permanent ban, the following countries also had banned phthalates in children's toys: Argentina, Austria, Cyprus,

Czech Republic, Denmark, Fiji, Finland, Germany, Greece, Italy, Japan, Mexico, Norway, and Sweden. In the EU and in these other countries, children still have soft toys to play with. Examples of alternatives include polyethylene, polypropylene and other non-PVC plastics, citrates, DINCH, and Grindsted soft-n-safe. Each of these alternatives is briefly discussed below.

Polyethylene, Polypropylene, and other non-PVC plastics. Safer cost-effective alternatives to phthalates exist, such as toys made from other types of plastic such as polyethylene or polypropylene that are considered safer than PVC and do not require the use of phthalates. Other alternatives include biobased plastics, thermoplastic elastomers, and ethylene vinyl acetate (EVA)[35].

These plastics do not require the use of phthalates since some are naturally softer, but many PVC products cannot be made without a plasticizer such as phthalates. The PVC-free plastics listed above also pose fewer lifecycle hazards because they are not chlorinated and do not release dioxins and furans during manufacture and disposal and are manufactured with chemicals that are less hazardous.

Citrates. Acetyl tributyl citrate (ATBC) is an important alternative to phthalates used to meet the ban in the European Union (EU). A risk assessment conducted by the EU Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) cleared citrates in 2004[36] for use in the EU as an alternative to phthalates. ATBC was found *not* to be a developmental or reproductive toxicant in studies in mice and rats.[37] Before these substitutes can be sold in the EU, studies must be conducted that show that the alternative does not pose any risk of cancer, reproductive or other health harm. The EU ban became permanent in 2005.

DINCH. Another commonly used phthalate alternatives in toys is called DINCH. There are no peer-reviewed publicly available scientific data on the toxicity of DINCH. However, the German chemical company, BASF, shut down its European DEHP production after the EU ban became permanent in 2005. Now BASF produces a new and profitable plasticizer line called DINCH after spending five million Euros on safety testing. DINCH is used in toys, food-contact materials and medical applications[38].

Grindsted Soft-n-Safe. The Danish company Danisco, one of the largest manufacturers of food additives in the world, introduced a phthalate alternative for toys – with no hormone disrupting effects –and other products that was approved for use in the EU in 2005. Danisco received The Danish Society of Engineers' Product Award for developing GRINDSTED® SOFT-N-SAFE, an environmentally friendly plasticizer based on vegetable oil for use in PVC[39].

Questions submitted by the Honorable Joe Barton

1. Please explain whether in describing phthalate alternatives as "cost-effective" you mean products made with alternatives are within the same price range as those products they are meant to replace.

Response: Yes, I meant that alternatives to phthalates exist that cost in the same general price range as those products they are meant to replace. The best example of this is the success in finding alternatives by companies selling toys in the EU and in other countries that have had a ban on phthalates in place for nearly a decade. This means that companies already have moved to safer alternatives. Ten years ago Mattel, Hasbro and Toys-R-Us, U.S.-based multinational companies who represent 60% of toy sales here, announced they would globally meet the EU standards. Other major retailers including Wal-Mart and Target are moving in that direction. Manufacturers that make phthalate free toys include Gerber, Little Tikes and the Natural Baby Catalogue. In fact, since the EU banned phthalates from toys, toy sales have increased, at a pace that exceeds their growth in the United States and prices look pretty much the same.[40]

2. Please explain whether phthalate alternatives have been tested to the same extent as phthalates, both in terms of volume of studies and studies conducted over time as it relates to long-term effects. Please explain whether these studies have proven the safety of phthalates alternatives to humans. If so, please provide specific examples.

   Response: There are now safe, viable alternatives in use in the EU and in other countries that have had a ban in place for nearly a decade. This means that companies already have moved to safer alternatives, with no reported rise in other dangers to children from those alternatives. Before these substitutes can be sold in the EU, studies must be conducted that show that the alternative does not pose any risk of cancer, reproductive or other health harm. This means that manufacturers can't simply substitute another toxic chemical for the one that is banned.

   In addition, the fact that other chemicals that might be used to soften plastic are less studied does not mean that we should wait to ban chemicals that we know are dangerous. If we followed that reasoning, we would never replace anything dangerous, for fear of what might come next. That's not sound logic for protecting consumers, especially the most vulnerable ones: infants and small children.

Questions submitted by the Honorable Diana DeGette

1. You testified that the statutory standards governing regulatory decisions by the Consumer Product Safety Commission (CPSC) are not those that should be used and are not protective of public health. Please expand on your testimony and why you believe this is the case.

   Response: The CPSC is notoriously understaffed and underfunded. This government agency has been cut to 100 inspectors to monitor some 15,000 products--including those lead-painted toys from China[41]. In order to ban a substance that the agency feels is a threat to public health, it must proceed through a rulemaking hearing, which in general, is a cumbersome, time consuming process that delays urgent action. This procedure was described in detail in the testimony of Dr. Michael Babich of the CPSC. Dr. Babich

described the burden of proof that the agency is required to meet in order to ban a substance. It is quite extensive and I refer you to his testimony for more details.

The rulemaking process that CPSC must go through requires regulators to look for scientifically irrefutable evidence linking phthalates, in this case, to human health. A simpler, more effective and protective approach would be modeled after the approach used by the EU which instead looks to make decisions by acting on the principle of preventing harm before it happens.

2. In what way or ways should the statutory standards pursuant to which the CPSC is authorized to regulate be improved by Congress in order to best protect consumers and the public health?

   Response: I would suggest that the CPSC be given the authority to adopt the approach used by the EU which makes public health decisions following the principle of preventing harm before it happens. Phthalates are one of the most heavily studied plasticizers and provide a clear example of how different the European and U.S. regulatory approach is when it comes to action on toxic chemicals. U.S. officials have had access to the same data, the same scientists and the same scientific journals as the Europeans. The only difference: Europe has decided to act. Robert Donkers, the EU's Environmental Counselor put it this way, "Unlike in the United States, we don't wait until we have 100 percent proof. "Rather, if there's fear, scientific suspicions, that a chemical could cause irreversible damage in the future, we don't wait to wait. By the time it's definitely proven, it could be much too late to do anything about it[42]."

   Industry opponents argue policymakers should ignore what they do know and instead focus on what we don't know. Yet, how much science do we need to tell us that chemicals regulated as hazardous waste by the EPA don't belong in chew toys and other toys our children play with everyday? The numerous recalls of children's toys over the past year have taught us that the government needs to step up and protect the health and welfare of our children. It took decades for industry to admit the dangers of lead paint, asbestos, and cigarette smoke. We shouldn't have to wait decades to get rid of toxic phthalates in toys. When we're talking about children's health, we should err on the side of caution, act on what we do know and prevent harm before it happens.

3. You testified that the burden of proof the CPSC must meet to issue regulations is different than the one the FDA must meet. Please expand on this distinction and include how standards governing the CPSC's ability to issue consumer protection regulations differ from those faced by other Federal agencies, those in the European Union (EU), and those faced by other foreign governmental entities.

   Response: As I mentioned in my oral response to questions at the hearing, I am not an expert in the regulations of the CPCS, or of the FDA. The point I was trying to make in my comments was simply that the path that FDA has to go through to ban a pharmaceutical drug is less burdensome that that facing the CPCS.

As stated above, a better approach is to give the regulating agency the authority to act to *prevent harm*, to avoid exposures to toxic chemicals without having to go through the exercise of trying to determine the level of risk that is "acceptable" to the government agency. No matter what this risk might be, it is always determined in isolation of the individuals or groups that bear the risks and thus this process is invariably inequitable. Instead, the U.S. should follow the lead of the EU who has adopted a precautionary approach to regulating toxic chemicals. This approach offers the agency the capacity to look at the evidence of toxicity of a substance, the availability of alternatives, and decide the best course of action to protect public health.

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