S. HRG. 110–1186

PLASTIC ADDITIVES IN CONSUMER PRODUCTS

HEARING

BEFORE THE

SUBCOMMITTEE ON CONSUMER AFFAIRS, INSURANCE, AND AUTOMOTIVE SAFETY

OF THE

COMMITTEE ON COMMERCE, SCIENCE, AND TRANSPORTATION
UNITED STATES SENATE

ONE HUNDRED TENTH CONGRESS

SECOND SESSION

MAY 14, 2008

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SENATE COMMITTEE ON COMMERCE, SCIENCE, AND TRANSPORTATION

ONE HUNDRED TENTH CONGRESS

SECOND SESSION

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PLASTIC ADDITIVES IN CONSUMER PRODUCTS

WEDNESDAY, MAY 14, 2008

U.S. SENATE,
SUBCOMMITTEE ON CONSUMER AFFAIRS, INSURANCE, AND AUTOMOTIVE SAFETY,
COMMITTEE ON COMMERCE, SCIENCE, AND TRANSPORTATION,
Washington, DC.

The Subcommittee met, pursuant to notice, at 10:05 a.m., in room SR–253, Russell Senate Office Building, Hon. Mark Pryor, Chairman of the Subcommittee, presiding.

OPENING STATEMENT OF HON. MARK PRYOR, U.S. SENATOR FROM ARKANSAS

Senator PRYOR. I will call the meeting to order. I want to thank everyone for being here. Senator Schumer is going to be here in just a minute. So I will go ahead and do my opening statement.

Just for everybody's knowledge, we have three panels today. We have, first, Senator Schumer and he has legislation. Second, we have a government panel, the FDA and the Consumer Product Safety Commission, and third, we have people who are—I am going to call them industry people or they are people that are familiar with this issue that are not inside the government. We look forward to hearing comments from everyone on this issue.

The purpose of the hearing today is to gather information and try to help us in the Senate start the process of getting the facts together and understanding this issue, understanding the facts and the science here. Like many of you, I have seen some media reports. Some of this has been on the sensational side. Some has not been. I think it is very important for the Senate and the Commerce Committee specifically to understand the science that is involved here.

So let me go ahead and open it up. Several Senators are going to be coming and going. There are other Committees meeting right now. So we expect to have several Senators here throughout the course of the hearing.

But again, I would like to say welcome to everyone.

I know that Senator Sununu will be here. I look forward to working with him on this issue, as well as other issues that we have been doing over the last couple years here.

We are here today to talk about plastic additives in consumer products. The focus of the hearing will include common chemicals found in plastics and consumer products, most notably phthalates and BPA, and their relevant scientific and health assessments by

leading governmental and nongovernmental bodies. I will also note that we are trying to gather relevant information from these experts and from people who understand these issues in an effort for Congress to, like I said before, get a better handle on this. So we are trying to, at today's hearing, get a wide range of input as our starting point, and then we will see where that leads us in subsequent weeks in subsequent hearings.

Again, there have been several news accounts of phthalates and BPA that are used in plastic consumer products. Many of these press reports talk about specific or potential health effects of exposure to these chemicals. I know that whenever you talk about chemical exposure, there are a lot of questions that come up about how the testing is done and whether you use high doses, low doses, how that testing process works. I am sure we will talk at least some about that today.

The panels here know what phthalates and BPA chemicals are, but let me go ahead and explain it to the general public because I think even Senators sometimes struggle with these scientific terms.

Phthalates are a common class of chemicals used in many household products to improve flexibility in plastics. Phthalates are primarily used to make PVC, a plastic used in many consumer products such as raincoats, vinyl furniture, flooring, medical and personal care products, and even in recreational and also lots of children's toys.

BPA is a chemical used to make polycarbonate plastics which are clear and nearly shatterproof. These plastics are used to make a variety of common products, including things like baby and water bottles, sports equipment, medical devices, CD's, household electronics. Any product that is made of hard, clear plastic likely includes BPA unless the manufacturer specifically states it is BPA-free.

The industry regulatory actions on these chemicals varies widely. California, the European Union, as well as numerous countries have banned certain phthalates in children's toys. Though no government entities have yet banned BPA, many states and Canada have begun initiatives to either regulate or ban BPA. So this is an emerging area when it comes to regulation, and again, it is important for us to understand what is going on out there.

Some of the larger companies like Wal-Mart, Toys "R" Us, IKEA, either have or will be phasing out the use of phthalates in some of their consumer products. I think Wal-Mart Canada and Nalgene, which makes these unbreakable kind of water bottles and these little containers, have begun phasing out the use of BPA.

Though the scientific studies for these chemicals are varied and robust, I believe it is essential for Congress to develop a clearer picture of the landscape for the use of these and other chemicals in plastics in consumer products. It is my hope that this hearing will allow us to get some of the facts straight.

It is also my hope that those here today can address not only the scientific studies of themselves and others with regard to phthalates and BPA, but also shed light upon alternative needs assessments and possible actions with regard to those other alternatives that exist in the marketplace.

It is imperative that Congress act judiciously when considering such vast reform to the regulatory nature of these consumer products and take into consideration not only the here and now but the future path that we might forge.

I very much look forward to hearing the testimony today. As I said, we will have other colleagues join us throughout the hearing. I look forward to their comments and questions and their input. I know that we will all have lots of questions and thoughts on this.

I would say this, that one of the things we talked about as we were on the floor passing the consumer product safety legislation, which we passed several weeks ago, was phthalates. That issue was hitting the news media about that time, and it raised a lot of discussion on the floor about what are phthalates, why are they used, how are they used, should we regulate them, should we ban them. I mean, we got into these questions.

One of the things that I learned is that there are many, many different kinds of phthalates, and some have been tested and tested and tested, and others we really do not know that much about. So we need to be careful in how we proceed, I think, because if we are not careful, if we ban one thing, some other phthalate may come on the market that may be more hazardous, more dangerous. So we just do not know. So we will talk about all those questions today.

And we are honored now to have Senator Charles Schumer of New York here. He has legislation. He is our first panel, and I know that he has a very, very busy schedule today. He is running between about 20 different stops he has to make this morning. So, Senator Schumer, thank you and welcome to the Subcommittee.

STATEMENT OF HON. CHARLES E. SCHUMER,
U.S. SENATOR FROM NEW YORK

Senator SCHUMER. Well, thank you, Mr. Chairman. Good morning. I want to thank you for holding this hearing. More importantly, I want to thank you for your really fine, exquisite leadership on these issues and CPSC reform. It has just been great. You have done all of this in a directed way where solving the problem is important, but a careful and measured way as well where you listen to all sides and try to balance the considerations. And I would just like to say, Mr. Chairman, I think the American people are lucky to have you in this position at this crucial time.

I would also like to thank Chairman Inouye for his work and determination and leadership on these issues as well. And I appreciate the Committee making some time to hear me on this issue because I care a lot about it and I think we have some things to do.

So I am here today to talk about bisphenol A, commonly known as BPA, and the legislation that I have introduced along with a whole bunch of my colleagues, the BPA-Free Kids Act of 2008.

The legislation is an important step in addressing the gathering storm of BPA safety. It will ban BPA in children's products, including baby bottles, sippy cups, and other toys. It is always a scary day when the health and safety of our children is called into question. Obviously, we want to protect them from harm and not expose them to possible danger.

When the National Toxicology Program of the NIH released their study that BPA could very well cause certain types of cancer and hormonal and developmental disorders, the world took note. The NTP cited studies showing that BPA can cause developmental problems in infants, particularly boys, which could lead to serious reproductive problems in later life. It also cited studies that indicated a possible link between childhood exposure to BPA and impaired neurological development.

When the report came out, the study, I heard from many concerned and confused parents around New York who read articles about the report, and they are now researching on websites and turning bottles over in stores and asking shopkeepers does this contain BPA. And now they are asking themselves was the bottle they used to feed their child safe. What about the teething ring? What about the sippy cup?

And the question I heard the loudest was why was the Government not doing anything about this. That was the biggest question we had, Mr. Chairman, and it was a good one because at the same time the report came out, we also read that Canada was taking action and banning this chemical in baby bottles. We heard that Nalgene—this is the water bottle maker from my home state. They are in Rochester, New York. They are a fine company, and they announced on their own they were discontinuing BPA produced bottles. We heard that Wal-Mart in your state, Mr. Chairman, was pulling its children's products containing BPA immediately from its Canadian stores and, by the beginning of the next year, from stores here in the states. Toys "R" Us took similar action. And in California, a ban on BPA in children's products is making its way through the State legislature.

Yet, here in Washington, we seem to have an FDA that was looking the other way, that was not taking the studies and concerns into account. I am now pleased that the FDA has initiated a task force to look into its prior approval of BPA and to determine if further action needs to be taken.

But I answer that right here and right now we cannot wait any longer. Congress must act. As I have said over the last month, when dealing with our vulnerable population, our children, it is better to be safe than sorry. We buy things for our kids to keep them safe: shatter-resistant sippy cups, chip-proof baby bottles. And then we find out later that the very products we thought would be safe could actually be much more dangerous for our children than the harm that they were intended to prevent.

So along with my colleagues, Senators Feinstein, Kerry, Clinton, Durbin, Menendez, and Boxer, I have introduced the S. 2928, BPA-Free Kids Act of 2008. The Act would ban BPA from children's products and mandate the CDC conduct a study into the negative effects of BPA on all age groups, including expectant mothers.

I would like to thank and commend my colleagues who have worked with me in creating this legislation, pushed this important issue. Particularly Senator Feinstein had some very important suggestions and we heeded most of them.

Mr. Chairman, parents always err on the side of caution when it comes to their kids' health. We think the law should do the same. My bill, if it errs, errs on the side of caution by banning the

use of BPA in all children's products, including toys, dishes, baby bottles, pacifiers, you name it. If it is made for children, it should not have BPA in it. Specifically, the bill would amend the Federal Hazardous Substances Act to include BPA for children's products and trigger all the prohibitions of the Act. In that case, BPA in baby bottles and other children's products could not be manufactured or sold. Parents will not have to worry whether the products their children put in their mouths could cause damage.

Let me be clear, Mr. Chairman. I think we have to look at eliminating BPA from a wide variety of products that all of us use in our daily life. If it causes harm, let us get rid of it. But I think it is important to focus first on children who we owe a duty to protect and shield from all harm, whether it is a sharp object or a toxic chemical. It is a similar philosophy that you and Senator Nelson and Senator Klobuchar, cosponsors of the CPSC Reform Act, took when addressing the problem of lead in toys. Just like lead, BPA has the potential to cause devastating health effects, and just like lead in children's toys, BPA should be banned.

Now, I am proud to say that this act has been endorsed by Consumers Union, Public Citizen, the Environmental Working Group, First Focus, Kids in Danger, and the Consumer Federation of America. All are groups whose mission it is to protect our children. I commend them for their work and appreciate their support.

Additionally U.S. PIRG has endorsed the bill, and I believe Ms. Hitchcock from the group is testifying before this Committee later this morning. And I would ask consent that their support letter be entered into the record.

Senator PRYOR. Without objection.

[The information referred to follows:]

Hon. MARK PRYOR,
Chairman,
U.S. Senate,
Subcommittee on Consumer Affairs, Insurance, and Automotive Safety,
Committee on Commerce, Science, and Transportation,
Washington, DC.

CONSUMERS UNION
CONSUMER FEDERATION OF AMERICA
KIDS IN DANGER
PUBLIC CITIZEN
NATIONAL RESEARCH CENTER FOR WOMEN & FAMILIES
U.S. PUBLIC INTEREST RESEARCH GROUP
May 13, 2008

Dear Chairman Pryor:

We are writing to thank you for holding a hearing this week to consider the effects of additives to plastics, including bisphenol-A (BPA) and phthalates. Our groups are deeply concerned about the potentially harmful health effects of both of these chemicals in consumer products. BPA is a common chemical found in many hard plastic products, including baby bottles, and phthalates are a family of chemicals used in toys, cosmetics, food packaging, and medical devices. We believe that the potential health and safety hazard associated with BPA and phthalates have escaped the scrutiny of our Federal regulators for far too long.

BPA

We know that bisphenol-A can leach from plastic containers and cans and into food and beverages, generating potentially significant human exposures. A recent study released by the U.S. Centers for Disease Control and Prevention (CDC) found that BPA was in the blood of 93 percent of Americans aged 6 and older. BPA raises particularly troubling health questions because it can affect the endocrine system, mimicking the effects of estrogen in the body. Experiments in animals and with human cells strongly suggest exposures typical in the U.S. population may increase

susceptibility to breast and prostate cancer, reproductive system abnormalities, and, for exposure in the womb and early childhood, a host of developmental problems. Concerns about early life exposures also extend to early onset of puberty in females, potential prostate problems in males, and obesity.

In May 1999, *Consumer Reports* magazine reported that BPA from polycarbonate plastic baby bottles leached into infant formula after the bottles were heated during testing. Based on these results, *Consumer Reports* scientists estimated that babies fed formula sterilized by heating in the bottle could be exposed to a BPA dose of about 4 percent of the amount that has adversely affected test animals in experiments conducted by Professor Frederick vom Saal at the University of Missouri, Columbia. The magazine pointed out that, although those levels may sound very low, safety limits for infant exposure can be set as low as 0.1 percent of the level that has adversely affected animals.

In the decade since *Consumer Reports* originally published this article, many new studies have substantiated the work of Professor vom Saal, as documented in recent reviews by expert committees at the National Toxicology Program and the Health Ministry of Canada. Unlike the Canadian government, which recently announced plans to ban major sources of BPA exposure, U.S. regulatory agencies have yet to act to protect the public.

The current U.S. Environmental Protection Agency daily upper limit for BPA, 50 micrograms per kilogram of body weight, is based on industry-sponsored experiments conducted in the 1980s. Some animal studies show adverse health affects from exposure of only 0.025 micrograms per kilogram of body weight, yet a polycarbonate baby bottle with room temperature water can leach 2 micrograms of BPA per liter. A 3-month-old baby drinking from a polycarbonate bottle may be exposed to as much as 11 micrograms per kilogram of body weight daily.

Aside from polycarbonate plastic bottles, BPA is also a food additive approved by the Food and Drug Administration (FDA), commonly used in the coatings for the inside of food cans. But a recent report by the National Toxicology Program (NTP) questioned previous FDA findings that BPA is safe for such applications. Their report, issued on April 15, 2008, expressed "some concern" based on animal studies that BPA might affect the neurological systems and behavior of infants and children. Among its conclusions, the NTP report states that, "the possibility that human development may be altered by bisphenol-A at current exposure levels cannot be dismissed."

Our organizations recently endorsed a bill introduced by Senator Charles Schumer recently, S. 2928, the "BPA-Free Kids Act of 2008." This bill will prohibit the use of BPA in all children's products, effective 180 days after its enactment. It will also require the CDC to study the health effects of BPA exposure in all age groups and pregnant women. We support this effort and feel it should focus on the products that have the greatest potential for causing human harm. Particularly due to the possible increased risks to small children and pregnant women, we strongly urge the removal of BPA from all products intended to contact food.

With such high consensus within the independent scientific community on the strength of evidence for adverse health effects associated with BPA exposure, we believe it is prudent—at a minimum—to remove BPA from children's products, until science can prove its safety.

Phthalates

Phthalates may be linked to developmental and reproductive health risks. The industry says that phthalates are safe, but some companies have removed them from cosmetics, for example, in response to public concern. California has also passed legislation banning phthalates in children's products.

In 2005, the CDC reported that it had found breakdown chemicals from two of the most common cosmetic phthalates in almost every member of a group of 2,782 people it examined. In rodent studies, phthalates have caused testicular injury, liver injury, and liver cancer. Another report in 2003 found that men with higher concentrations of two phthalate breakdown products in their urine were more likely to have low sperm count or low sperm motility.

With such serious concerns about the impact of phthalates on our health, and because of the ubiquity of these chemicals in our products, we believe Federal agencies must also examine and act upon independent, unbiased science about all of the potential harms associated with phthalates in order to protect the public health.

Again, we appreciate your Subcommittee's work in examining BPA and phthalates. We look forward to continuing to work with you and the members of the Subcommittee in the future.

Sincerely,

DONALD L. MAYS
Senior Director, Product Safety and Technical Public Policy
Consumers Union

AMI GADHIA
Policy Counsel
Consumers Union

NANCY A. COWLES
Executive Director
Kids in Danger

DAVID ARKUSH
Director, Congress Watch
Public Citizen

ELLEN BLOOM
Director, Federal Policy
Consumers Union

RACHEL WEINTRAUB
Director of Product Safety and Senior Counsel
Consumer Federation of America

ELIZABETH HITCHCOCK
Public Health Advocate
U.S. Public Interest Research Group

PAUL BROWN
Government Relations Manager
National Research Center for Women & Families

Senator SCHUMER. These groups have told me that the BPA-Free Kids Act of 2008 is a huge step in the right direction of protecting children from potential neurological or reproductive harm.

We will hear from others, I am sure, who are going to say today that BPA is safe and this entire outcry has been blown way out of proportion. And my response is that Congress should not gamble with our children's health. If there is a significant chance that this may cause harm, particularly in children, then we ought to err on the side of caution.

In closing, I believe that we in Congress owe it to parents to give them the peace of mind that this bill would provide. There are alternative chemicals and other products that can be used, as shown by the speed by which companies like Nalgene and Wal-Mart and Toys "R" Us moved, and I hope, Mr. Chairman, that in the coming months, this Committee will have the opportunity to mark up this bill and it will be passed into law. Obviously, I look forward to working with you and the Committee to move our legislation, make improvements that you might see fit.

And last but certainly not least, I want to thank you and the Ranking Member for allowing me the opportunity to speak here today.

Senator PRYOR. Well, thank you, Senator Schumer. It is always good to have you here, and thank you for your interest in this and your leadership.

I do not have any questions about your legislation at this point. Do you?

STATEMENT OF HON. JOHN E. SUNUNU, U.S. SENATOR FROM NEW HAMPSHIRE

Senator SUNUNU. No, I have no questions. I certainly want to thank the Senator for being here and thank the Chairman for putting together the hearing.

There is no question that we need to understand the role and responsibility of the agencies that are entrusted with the protections Senator Schumer talked about, the FDA, the Consumer Product Safety Commission, their role and responsibility in understanding the impact and effects of not just BPA, but any additives and

chemicals that are included in plastics, especially those intended for products that are used by children. They are the most vulnerable population. They are the ones who are most likely to be affected by even low dosages or low levels of exposure.

We also want to make sure that we are doing everything possible at the Federal level to better understand those impacts, whether it is research that is funded through agencies like the NIH, or research that is being encouraged or funded in the private sector. We need to have an honest, clear-headed assessment of what the health effects are, and what the risks are even if the risks are small. Oftentimes even small risks warrant taking action as an insurance policy against our lack of knowledge.

So I thank the Senator for being here and look forward to the testimony of our key witnesses.

[The prepared statement of Senator Sununu follows:]

PREPARED STATEMENT OF HON. JOHN E. SUNUNU,
U.S. SENATOR FROM NEW HAMPSHIRE

Mr. Chairman, thank you for holding today's hearing.

Lately, many Americans have heard and read a lot about phthalates and bisphenol A (BPA), but for most, these two chemicals generate a tremendous amount of confusion.

There are scientific studies that conclude both are perfectly safe, and other studies that indicate possible concern.

Consumers see retail giants Wal-Mart and Toys "R" Us tell their suppliers that they will no longer sell toys with phthalates and baby bottles with BPA and they wonder: if they're taking action, then maybe there is some health impact after all. Or, are they responding to market forces.

American consumers want to know:

- Are these chemicals safe?
- Are calls for their removal from products justified?
- Are there alternatives that are safer and more effective?

Consumers are receiving conflicting data over what's safe for their families, and they want to be able to separate fact from fiction.

The sheer ubiquity of plastics in our society necessitates a closer look; to make sure the products consumers are purchasing, and particularly, eating and drinking from, are not harmful.

It is my hope we are able to shed some light on this important issue today, and I am quite interested to hear what our witnesses have to say.

Thank you, Mr. Chairman.

Senator PRYOR. Thank you.

Senator SCHUMER. I thank both of you.

Senator PRYOR. Thank you, Senator Schumer.

With that, what we will do is we will call up our second panel, and that would be the two government witnesses. And I will just do a very, very brief introduction. If you all want to come up and take your seats and get your microphones adjusted there, that would be great.

First we will have Dr. Norris Alderson, Associate Commissioner for Science, the Food and Drug Administration, and second we will have Dr. Marilyn Wind, Deputy Associate Executive Director for Health Sciences, Consumer Product Safety Commission. Dr. Alderson, do you want to go first?

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

Dr. ALDERSON. Good morning, Chairman Pryor and Members of the Subcommittee. I am Dr. Norris Alderson, Associate Commissioner for Science at FDA. Thank you for providing an opportunity to discuss the FDA's ongoing work regarding the safety of bisphenol A, or BPA.

Last month, FDA Commissioner Andrew von Eschenbach formed an agency-wide BPA Task Force, which I chair, to conduct a review of the concerns raised in recent risk assessments of BPA. That task force is undertaking a cross-agency review of 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 will note, however, that individuals who, nonetheless, have concerns about BPA may turn to alternative products in the marketplace. For example, alternatives to polycarbonate baby bottles such as those made from glass are widely available.

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 the action needed.

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 in inner linings of food and beverage cans. These food contact substances have been regulated by FDA for many years and are enforced by sections under Title 21.

Small residual amounts of trace 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. 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 that FDA regulates, not just the ones I have mentioned. We are already focusing on specific concerns raised by reports of the National Tox Program at NIH.

In November 2007, NTP's Center for the Evaluation of Risks to Human Reproduction released a report by a panel of experts. The opinion reached by the experts was that they had some concerns for children regarding neural and behavioral effects. They also had minimal concern for BPA exposure to these populations for the effects on the prostate gland, mammary gland, and early female puberty.

NTP subsequently issued a draft report, and they iterated the same thing relative to the behavior, but they also raised their concern on the mammary gland and the early female puberty.

These included new data which we are all continuing to review. And these lead us to conclusions that the currently available evi-

dence provides little evidence that there are issues, but it also raises a number of uncertainties which the NTP brief identified.

We have studied the reports and conclusions of NTP's expert panel and we are actually reviewing the draft. In fact, members of the BPA Task Force will be meeting with the NTP staff this week to discuss their findings and get a better understanding of how they came to their conclusions.

Also, I should tell you, Senator, FDA's National Center for Tox Research is discussing with the NTP staff yesterday and today both BPA and phthalates.

Although the FDA has been actively surveying data on BPA for many years, this form of assessment began in early 2007. We initially focused on the low-dose effects and have concluded that the current exposure to adults and infants is safe. Although FDA's reliance on these studies have been questioned because they were funded by industry, they were considered pivotal by FDA in our review of the data for a number of reasons. FDA's findings thus far are underscored by the conclusions of two risk assessments 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. FDA does not now have a comprehensive inventory of products that contain phthalates. We do know it is a component of the compounds used in certain medical products and that brings risk-benefit factors into play. FDA primarily through NCTR is conducting research to address uncertainties in our understanding of the potential health risks posed by exposure to phthalates.

In conclusion, let me re-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 chemical compounds or the products in which they are found are never set in stone. They are always subject to review or revision when new data or a better analysis become available. At the end of the day, FDA's goal is always to act within our authority and protect the public health.

Thank you for the opportunity to testify today, and I will be happy to answer any questions you may have.

[The prepared statement of Dr. Alderson follows:]

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

Introduction

Good morning, Chairman Pryor 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 and Health Canada, as well as interested public health advocates, FDA believes it is important that consumers have accurate and up-to-date information about BPA. We have established a link on our home page, at *http://www.fda.gov,* 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 under-

taking 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

Section 409 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) requires that chemicals undergo pre-market approval by FDA if they are reasonably expected to migrate to food. 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. 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 BPA 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 were based on realistic, but still conservative, use scenarios for both adults and infants.

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 multigenerational 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 and the BPA Task Force, and we will take appropriate action, if warranted, at the completion of our review.

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. FDA's work in assessing the safety of these products is never truly final, and if our continuing review of all available data leads us to a determination that the current levels of exposure to BPA 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.

Senator PRYOR. Thank you.

Dr. Wind?

STATEMENT OF DR. MARILYN L. WIND, DEPUTY ASSOCIATE EXECUTIVE DIRECTOR FOR HEALTH SCIENCES, U.S. CONSUMER PRODUCT SAFETY COMMISSION

Dr. WIND. Good morning, Mr. Chairman and Members of the Subcommittee. My name is Dr. Marilyn Wind and I am the Deputy Associate Executive Director for Health Sciences at the U.S. Consumer Product Safety Commission. I am pleased to come before this Committee today to testify and to answer your questions regarding phthalates and bisphenol A.

Phthalates are chemicals used to soften 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, or the FHSA. Under the FHSA, CPSC must consider both the toxicity of, as well as the exposure to, a product in order to designate it a hazardous substance. Children's products containing a hazardous substance are automatically banned by operation of law.

Since the early 1980s, the CPSC has investigated, researched, and monitored phthalates used in consumer products under the agency's jurisdiction. In the early 1980s, the primary phthalate used in children's products was di-(2-ethylhexyl) phthalate, or DEHP. After a National Toxicology Program bioassay indicated that DEHP caused cancer in rodents, the Toy Manufacturers of America representing their member companies agreed to voluntarily cease using DEHP in toys intended to be mouthed, and subsequently, a ban of DEHP was incorporated into the ASTM toy

standard. DEHP was replaced with another phthalate, diisononyl phthalate, or DINP.

Chronic 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. 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, staff at that time recommended that the commissioners convene a Chronic Hazard Advisory Panel, or CHAP, to evaluate whether there are chronic hazards associated with exposure to DINP and what, if any, risk is posed. The staff further recommended: one, that the Commission conduct an extensive observation study of children's mouthing behavior to better understand the exposure issues; two, to develop a better laboratory method to measure the migration of DINP from products; and three, to test additional products intended for children under 3 years of age for phthalates. The Commission approved all of these staff recommendations.

A CHAP was convened and issued its report to the Commission on June 15, 2001. Staff also completed all the studies that the Commission had approved by 2002. Taking all of this information together, 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. Based upon this analysis, the Commission voted 3 to 0 on February 21, 2003 to deny a petition which requested the ban of PVC in all toys and other products intended for children 5 years of age and under.

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

With regard to bisphenol A, or BPA, this is a chemical used in the manufacture of polycarbonate plastics and epoxy resins. The greatest potential for human exposure to BPA is from contact items. The recent in-depth peer review conducted by the National Toxicology Program Center for the Evaluation of Risks to Human Reproduction stated that diet accounts for the vast majority, 99 percent, of human exposure. If BPA migrates out of a food contact surface into food, it is considered an indirect food additive and would be under the jurisdiction of the Food and Drug Administration.

Polycarbonate used in pacifier shields, helmets, protective gear such as goggles and chin guards, as well as other products, would fall under CPSC's jurisdiction. Polycarbonate is used in these prod-

ucts because it is very hard, unbreakable, and a sturdy plastic. There would be no exposure expected from helmets, goggles, other protective gear, compact disks, or electronics. The use of polycarbonate in pacifier shields prevents the shield from shattering when a child falls. Polycarbonates used in protective gear prevents head, eye, and bodily injury. Beneficial uses of polycarbonates such as these should be considered when acting to ban bisphenol A from children's products.

I am pleased to have the opportunity to testify today and welcome your questions.

[The prepared statement of Dr. Wind follows:]

PREPARED STATEMENT OF DR. MARILYN L. WIND, DEPUTY ASSOCIATE EXECUTIVE DIRECTOR FOR HEALTH SCIENCES, U.S. CONSUMER PRODUCT SAFETY COMMISSION

Good Morning, Mr. Chairman:

My name is Dr. Marilyn Wind, and I am the Deputy Associate Executive Director for 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 1980s, 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.

In the early 1980s 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 3 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

[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.

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 5 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 percent. Because phthalates are ubiquitous, the level of 0.1 percent would be a contamination 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 percent; that is 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 percent.

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 Risks to Human Reproduction (CERHR) stated that diet accounts for the vast majority, 99 percent, 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). I am pleased to have the opportunity to testify with Dr. Alderson from FDA today, and I welcome your questions.

U.S. CONSUMER PRODUCT SAFETY COMMISSION
Washington, DC

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 5 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, February 26, 2003

Mr. JEFFREY BECKER WISE,
Policy Director,
National Environmental Trust,
Washington, DC.

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 italic)*

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 5 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 5 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 5 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 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 5 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

[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).

Commission to take the requested actions with respect to DINP in PVC toys and other products intended for children 5 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 5 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, February 20, 2003

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

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 5 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.

U.S. CONSUMER PRODUCT SAFETY COMMISSION
Washington, DC, February 21, 2003

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

I am voting to deny the petition to ban polyvinyl chloride in products intended for children 5 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 staffs 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 staffs 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.

Senator PRYOR. Thank you.

Dr. Alderson, let me start with you, if I may. Is it your view that the FDA should do more testing at this point?

Dr. ALDERSON. Senator, the meeting that I referred to yesterday at NCTR was between staff of FDA as well as staff of the National Tox Program. FDA and particularly NCTR is what I call a partner in the NTP program, as we are one of the participating agencies which the NTP program serves in terms of the products we identify we need more information on.

So the meeting ends today at noon, but I can tell you on the agenda the first thing yesterday morning was BPA. That was the first agenda item. They reviewed a number of proposed studies that will be considered, particularly in the pharmacokinetic studies to look at these low-dose issues that you referred to earlier in your statement. There were other things considered that need more review.

But the short answer to your question is, yes, we will be doing additional research on BPA directed by the things that have been identified as uncertainties in the NTP draft report.

Senator PRYOR. Now, for clarification, let me just make sure that we understand your testimony, and that is, you said at the present time, there is no reason to stop using BPA because I guess the risks are either not present or they are acceptable.

What about on phthalates? Have you come to a decision on phthalates?

Dr. ALDERSON. Phthalates is a little different. The Center for the Evaluation of Risks to Human Reproduction in early 2000 also did a similar type of report on phthalates that we now have before us on BPA. In that review, the CERHR also agreed with FDA's current position, that other than in infant males, we do not have that much concern, but at NCTR today ongoing there is a non-human primate study looking at this issue. So we are addressing the issues that we know about either currently or they are planned.

Senator PRYOR. Please explain to the Subcommittee in layman's terms the low-dose issue. I have heard it called the low-dose hypothesis. Could you explain what we mean by that, and is that controversial?

Dr. ALDERSON. Well, let me start with the high dose first. The studies that are referred to in the NTP report referencing to high doses—in fact, I think the NTP brief says there are no controversies associated with the high doses. Everyone agrees there are effects there that we need to be concerned about.

But when you come to the low doses, the endpoints that are being considered in terms of effects, there is not agreement between scientists. We have a number of reviews. If you look at those, there are disagreements between those reviews on whether there are effects or there are not effects. We believe that at this time the recent two studies that are referred to as the industry-supported studies are the best regulatory approaches in terms of data to address the low doses.

Now, having said that, we do not consider those to be the final answer. That is because, I think, we agree that there are some issues still remaining there in terms of the effects. There are uncertainties regarding these low-dose effects; *i.e.,* the studies need to be conducted to address those particular endpoints. They need to be designed such that you would have enough power to reach conclusions. We do not see that in a lot of studies other than these two multi-generation studies, the most recent studies that have been referred to.

So there are uncertainties. It is not definitive. The science associated with how do you address those particular endpoints—there is not agreement among the toxicological community on how to do that.

Senator PRYOR. Great. I was planning on doing one round, but I may reserve the balance of my time for follow-ups.

Senator Sununu?

Senator SUNUNU. Thank you very much.

You mentioned two major intergenerational studies. How many studies have been done in total that you look at to draw the conclusion that you made that BPA is safe?

Dr. ALDERSON. Senator, we have looked at all the studies in the literature, and there are hundreds.

Senator SUNUNU. It numbers in the hundreds. I just wanted to get a rough idea of whether we are talking about——

Dr. ALDERSON. Many hundreds.

Senator SUNUNU.—a dozen or a couple of dozen, but certainly more than——

Dr. ALDERSON. Keep in mind this is a material that has been on the market or been used for now probably at least 25 years. So there is a wealth of information out there.

Senator SUNUNU. —understood.

And approximately how many of those or what portion of those studies look not just at health effects, but specifically focus on the health effects of children?

Dr. ALDERSON. I have no way of answering that, Senator.

Senator SUNUNU. If you could try to get that information for the record just so that we have——

Dr. ALDERSON. We will try to get you an answer on that.

Senator SUNUNU.—a general understanding of what the target is.

Second, with regard to the high and low exposure, high and low dose, what does that mean? When you say a high dose, what is the level, and when you say low dose, what is the exposure level relative to the higher figure?

Dr. ALDERSON. I do not know whether I have it, without looking in the NTP report. Here are some numbers that I have. For high dose, I think the NTP report or brief refers to something greater than 50 milligrams per kilo of body weight per day. For a low dose, we are talking about doses equal to or less than 5 milligrams per kilogram per day. This is what the NTP report refers to.

Senator SUNUNU. OK.

What do you think the basis is for those who have opposed your finding? What argument are they making and how would you respond to their argument? Clearly, there is a difference of opinion

here and we need to at least understand what the basis is for that difference.

Dr. ALDERSON. It is FDA's view that the basis for this is what we would normally ask for to support a decision on safety of this type of material. We would want to see a study that is specifically designed to address a particular endpoint that had been identified in perhaps another study where we have multiple doses, we use the correct model, *i.e.,* the correct species, there is appropriate statistical analysis conducted on it, it is conducted under GLP standards. There is a whole gamut of standards that FDA prescribes when we are looking to make a decision on safety, and that is the same type of information that we recommend to a sponsor who comes in and tells us what do you need.

Senator SUNUNU. But you agree that there is a value in doing additional research and additional evaluation, including many of those criteria?

Dr. ALDERSON. There is no question that many of the other studies that are out there in the literature—we would consider them hypothesis-testing. They are very important to us because they identify potential endpoints that need to be further evaluated, particularly as it relates to levels where we see no effects.

Senator SUNUNU. Dr. Wind, obviously, the difference between a high-dose level and a low-dose level, 50—what is it?

Dr. ALDERSON. Fifty milligrams per kilo.

Senator SUNUNU. Fifty milligrams versus 5 milligrams. There is some significance there.

You talked about the level of material that is actually included in products, not the exposure level or the dose, but the threshold of one-tenth of 1 percent phthalates in the products and suggested that that might be impractical to set as a standard, to measure as a standard because of the physical nature of the manufacture of the products.

Could you speak a little bit more about that and let us know if we were going to set a standard in order to minimize the risk, or minimize the exposure, from a manufacturing or testing standpoint what might be more practical?

Dr. WIND. I think that when I spoke about the amount of phthalate that we found in products when we tested them, that was the amount that is needed to make the product flexible. So it is intentionally added to the product. You do not add .1 percent of phthalate to a product. Phthalates are ubiquitous because they're used in everything, and so that would be a contamination level.

When the ASTM established their standard for di-ethylhexyl phthalate——

Senator SUNUNU. I am sorry. When you used the phrase "contamination level," though, are you suggesting that it is an impractical standard because some contamination at that very low level is almost inevitable——

Dr. WIND. Yes.

Senator SUNUNU.—or that that is an appropriate level because you would not want to have contamination at that level?

Dr. WIND. No.

Senator SUNUNU. You need to be clear.

Dr. WIND. I am suggesting that that level is impractical because contamination is going to occur.

When we looked at the phthalates—at DINP, because that is the only one that we have done extensive work on, even with the high levels, you did not see a health risk.

When ASTM set the level for the DEHP standard, they set it at 3 percent of intentionally added DEHP to the product. So I think that the intentionally added is an important concept.

Senator SUNUNU. I have one more question, Mr. Chairman, and I apologize for going over, but I am going to have to depart for another hearing.

But I do want you to address the concern you raised about the impact of products that are designed as protective products, shin guards, eye goggles, other protective gear, if there were a ban put into place. For those protective products, are there alternatives to BPA, and have you tried to quantify what the impact might be in terms of health or safety if there were a ban put in place?

Dr. WIND. We have not tried to look at the impact at this point. I do not know what would be used. What I do know is that since there is no exposure to BPA from something like a helmet or safety goggles, that no exposure means no risk.

Senator SUNUNU. And those products that you mentioned would be affected by the legislation as written——

Dr. WIND. Yes.

Senator SUNUNU.—because it bans it in all products no matter what the impact or exposure might be from that product.

Dr. WIND. Yes.

Senator SUNUNU. Thank you very much.

Thank you, Mr. Chairman.

Senator PRYOR. Thank you.

We have been joined by Senator Bill Nelson and Senator Amy Klobuchar. Senator Nelson, you are next.

STATEMENT OF HON. BILL NELSON, U.S. SENATOR FROM FLORIDA

Senator NELSON. Thank you, Mr. Chairman for holding this hearing on the potential risk that we see here. Mr. Chairman, I want to pick up exactly where Senator Sununu was going on this.

Dr. Wind, since there is the voluntary industry standard called ASTM F–963 and it bans phthalate DEHP in pacifiers, rattles, and teethers, is the Commission going to consider not a voluntary standard for the industry, but a mandatory rule?

Dr. WIND. For DEHP?

Senator NELSON. For pacifiers, rattles, and teethers.

Dr. WIND. Pacifiers are no longer made out of PVC. They are made out of latex rubber and silicone rubber.

Senator NELSON. Anything that can go into the child's mouth you are going to consider mandatory?

Dr. WIND. Our statute requires that if a voluntary standard is in place and is effective, that we not do a mandatory standard. DEHP at this point is not used in children's products.

Senator NELSON. So you support the voluntary but not a mandatory. Is that what you said?

Dr. WIND. No. What I am saying is DEHP is not used in children's products at this point. So there is no exposure to DEHP.

Senator NELSON. It is not used in rattles and teethers?

Dr. WIND. No.

Senator NELSON. Is it used in any small items that can get into a child's mouth?

Dr. WIND. Children mouth a lot of things, so it probably is, but they are not toys.

Senator NELSON. Let me ask you this. We have put it as a mandatory standard in the Consumer Product Safety Commission.

Dr. WIND. Right.

Senator NELSON. Is your leadership going to support the position in our bill?

Dr. WIND. Of course, whatever Congress puts in the bill we will support because that is what we——

Senator NELSON. If it is the law.

Dr. WIND. If it is the law.

Senator NELSON. What will your agency recommend to the President on a veto or signing the bill since it has the mandatory standard?

Dr. WIND. I am just a scientist. So I cannot answer that question.

Senator NELSON. So you cannot speak for the leadership.

Dr. WIND. Right, yes.

Senator NELSON. OK. I am just a little country lawyer, but I have to speak out for my constituents and a lot of these little babies that get hold of these products.

Let me ask you since you note in your testimony that the Commission's actions addressed phthalates during 1998 to 2003, but since then there have been a number of studies that have come out and some countries, indeed, a state that considers itself a country, the State of California, has banned the use of certain phthalates in toys—so it would seem that this ought to be at the top of the agenda without it all being voluntary.

Dr. WIND. The phthalate that children are exposed to the most is diisononyl phthalate, DINP. That is the one that we did extensive work on back in the late 1990s and early 2000 and the one where the Commission denied the petition to ban it. There have not been any studies on DINP that have come out since then that would change the scientific information and conclusions that we made from that study.

We worked with our colleagues in the European Union because we did not understand how they reached the conclusion that DINP should be banned, and we had extensive discussions with them. The reality was that their risk assessment came out with the exact same acceptable daily intake that ours did.

The difference between the two studies was we used our exposure data which we derived from a very extensive behavioral observation study. They picked out a number that was vastly larger in terms of exposure that is not justified by the current research, and that is how they came out with a risk of injury.

Senator NELSON. So you are disagreeing as a scientist with some of these studies that have said phthalates and BPA may not be suited for use in certain toys in children's products.

Dr. WIND. I am not making a comment about BPA because——

Senator NELSON. OK. That has got BPA in it. What do you think about that?

Dr. WIND. That is Food and Drug Administration's jurisdiction. So I will not comment on that.

Senator NELSON. All right. Then let me ask Dr. Alderson. Many of these studies have focused on the effects. So has FDA, EPA, CPSC, or any other agency had studies that show the combined impact of these chemicals on adolescent development?

Dr. ALDERSON. When you say "combined," I want to make sure I understand the question. We have studies that we have reviewed the literature, a lot of studies relative to each of these materials separately. I am not aware of any studies—that does not mean they do not exist, but I am not aware of any that we have discussed internally in FDA where there have been cumulative effects looked at in terms of studies that had, for instance, BPA and DEHP in both.

Senator NELSON. Well, let us do not confuse the question. Omit—strike from the record, Mr. Chairman, the word "combined." All right. Now will you answer the question?

Dr. ALDERSON. Yes, sir.

There are ongoing considerations of the data relative to BPA. Recent events with two documents from NTP released last month, an NTP brief draft document, that will be peer-reviewed next month by the NTP—that is the current document that we at FDA are considering. We have a task force looking at the implications of that.

There were two issues raised in that document of some concern at the low-dose levels. They in their review looked at all the data, as we understand it, that were available, including the two low-dose multi-generation studies, one in rats and one in mice. So there is a lot of literature relative to BPA.

Senator NELSON. What are you going to do about it?

Dr. ALDERSON. Well, we are taking a look at that. We also need to wait until the NTP peer review is completed, which will take place on June 11th, and they will issue their final monograph this fall as to whether those areas of some concern are sustained through the peer review process.

Senator NELSON. What do you think CPSC ought to do about it?

Dr. ALDERSON. What I think CPSC ought to do?

Senator NELSON. Are you not there to protect the interests of the public?

Dr. ALDERSON. But as it relates to the FDA regulated products, *i.e.,* those food contact materials and materials in food cans.

Senator NELSON. Right, affecting the consumer safety and health.

Dr. ALDERSON. At this point, Senator, we think they continue to be safe. We have not seen data where we would reach the conclusion that they are unsafe.

Senator NELSON. And "they" in this answer is who?

Dr. ALDERSON. FDA.

Senator NELSON. What products?

Dr. ALDERSON. Well, we are talking about specifically food contact materials, *i.e.,* baby bottles, food packaging. We are also talking about liners that are in metal cans.

Senator NELSON. How about that?
Dr. ALDERSON. Yes, sir.
Senator NELSON. That is safe.
Dr. ALDERSON. As far as we are concerned. Today we have no reason to change our position on it.
Senator NELSON. Even though it has got BPA.
Dr. ALDERSON. Even though it has got BPA.
Senator NELSON. OK. And there are no studies that are saying that the BPA in there in that bottle right there is unsafe?
Dr. ALDERSON. I do not know about that specific bottle, but bottles similar to that one.
Senator NELSON. Dr. Alderson, you know what I am asking. Quit straining at gnats. Are there any studies?
Dr. ALDERSON. The studies we have seen, studies FDA has conducted on leaching of this material from this type of product would tell us unless you would subject it to very harsh conditions, *i.e.,* continuous boiling or something like that, that the amount of BPA that is going to leach into the food that may do it in that bottle is safe.
Senator NELSON. Thank you, Mr. Chairman.
Senator PRYOR. Senator Klobuchar?

STATEMENT OF HON. AMY KLOBUCHAR,
U.S. SENATOR FROM MINNESOTA

Senator KLOBUCHAR. Thank you, Mr. Chairman, and thank you for holding this important hearing.
Dr. Alderson, a recent article in *The New York Times*—one scientist, when looking at these studies of the plastic additives, was quoted as saying, "companies and states are taking leadership where the Federal Government isn't."
And some examples of that—Senator Nelson mentioned the State of California. Kaiser decided the evidence that the phthalates were leaking into intravenous bags were enough to start looking for other options, and they gathered a team of experts to come up with medical gloves and other medical supplies that were free of phthalates. And as of 2004, Kaiser has been rolling out only PVC-free products, including intravenous bags and tubes.
Many companies are not waiting for Federal regulation and are already selling products that conform to the stricter chemical standards that you find in the European Union, Canada, and Japan.
My question is this. At what point should the Federal regulators step in? Why would companies like Kaiser make this decision and the Federal Government is not doing anything? What message are we sending to consumers when they read about BPA and phthalate studies, but see that the Government has not done anything?
Dr. ALDERSON. Senator, the FDA often finds itself in this position. We have standards that we ask of industry to give us as it relates to safety and efficacy of products. In this case, you are talking about products that were approved many years ago, and because they are food additives, a manufacturer can take that product and start marketing it without any preclearance as long as it puts that material in there in accordance with the regulation.

Now, having said that, as literature becomes available on these type of chemicals in the products, particularly food packaging materials, we are continuing to look at it. And where there are data that become available that raises our concerns and they meet a regulatory standard in terms of quality of that data where it is designed to address in this case safety, we will take action. But as I have said previously, at this point in time, the data that we have seen does not lead us to change our position on how we look at the safety of either BPA or DEHP.

Senator KLOBUCHAR. Another example—and I know that Senator Nelson was talking to you about these bottles. Nalgene has started phasing out the use of BPA in their water bottles—and this is one of those old water bottles—because of these studies that have come out showing this additive leaking into food and beverages. In their new water bottles—and actually one member of my staff actually just ordered this new Nalgene water bottle. It looks similar and, however, do not leak.

So where this research has shown that by using boiling water in one of these to—which by the way, I was amused to find out as we prepared for this hearing—just yesterday I used one of these water bottles, Mr. Chair, and ran it under really hot water under the faucet for quite a while because I was too lazy to put it in the dishwasher. It did strike me that if I had a choice and I knew that this was going on, that this company was actually phasing these out, that I would probably not want to take the risk, that I would probably use this water bottle.

So what I am thinking about is these parents with baby bottles and knowing that there is some risk out there. Do you not think that they should be somehow—at least be some requirement that these things be labeled so if you guys are not going to regulate them, that they can at least make their own choice based on what they are seeing in some of these studies?

Dr. ALDERSON. Senator, we at FDA have put out in our announcements regarding this issue since this came out last month that there are alternatives, particularly as it relates to baby bottles, *i.e.,* glass. Those are there for people to see. We have also pointed out how you can determine whether BPA is in these bottles by looking at the recycling notification on those bottles.

Senator KLOBUCHAR. That sounds really hard for a mom with a 12-year-old and you are trying to get them off to school. We are supposed to look at recycling requirements?

Dr. ALDERSON. That is what the current regulation and laws require of us.

Senator KLOBUCHAR. But we are looking at maybe changing the laws and requirements to make it easier. That is why we are having this hearing.

Dr. ALDERSON. I do not think FDA would object.

Senator KLOBUCHAR. My next question is this: If these companies are starting to phase these out and they are concerned about some of this leakage themselves, should the Federal Government not be more concerned and moving more quickly to do something about it? Because maybe not every other company is going to start taking these off the market. They are just going to keep using the old ones.

Dr. ALDERSON. Senator, in FDA's consideration of safety of products, we feel we are obligated to use the best science to make those decisions. The process and the science that we follow—we have got a prescribed way we go about determining safety, and it is based on the current science as it relates to these type of materials. It is rated to the current science on what is the best approach to determine safety without going to humans because we are not going to be able to do human studies to make these determinations.

Senator KLOBUCHAR. Does the National Toxicology report released this month raise some concern about the effects of BPA on infants and children?

Dr. ALDERSON. It does. It raises concerns but that——

Senator KLOBUCHAR. The European Union and Canada and these others countries have actually done something about that, and we are just concerned.

Dr. ALDERSON. Well, even the Canadian report, in reading it, they point out there are really uncertainties in the data that they have reviewed. They also point out the need for further research.

The EU, in communications we have had with them this week—they are raising no concerns about the NTP report or the recent studies. Their position is being maintained.

Senator KLOBUCHAR. But you are concerned about the report and what it says.

Dr. ALDERSON. We are concerned about it. That is the reason at FDA we have a task force that we are looking across all the agencies at any of our products that have BPA in it.

Senator KLOBUCHAR. I am just again thinking of these parents. They can choose one duck or the other duck, and one duck has phthalates and one duck does not. I think they would like to make that choice themselves, and we are not giving them the tools to do that.

Thank you very much.

Senator PRYOR. Thank you.

Senator Nelson?

Senator NELSON. Dr. Alderson, you said in my previous commentary with you that a bottle like this with BPA is safe. So you would suggest to a young mother who would have a baby bottle made with BPA that she wants to heat up the formula, that you would recommend that she can use that bottle with BPA as opposed to a bottle without BPA. Is that your recommendation?

Dr. ALDERSON. I think our recommendation would be that she not heat the formula in that polycarbonate bottle containing BPA, that she heat it in another source and let it cool and then put it in the bottle.

Senator NELSON. All right. Has such a recommendation been made by the FDA?

Dr. ALDERSON. I think that recommendation is in our recent announcements regarding our position as we follow the NTP brief draft. We pointed out that those alternatives are available, and I think we have said—and I do not have it in front of me, Senator—that we talked about there are alternative ways to prepare this. Certainly in our research, we have pointed out that boiling materials in these bottles is not recommended. And I do not think the manufacturers even recommend that.

Senator NELSON. But they have got a choice. A consumer has a choice if they know the difference between a bottle with BPA and one that does not have BPA. And so the question that is just begged that we have to ask, representing our constituents and wanting their safety of the very agencies that are charged with protection of the consumers, is, is the consumer being advised by the Executive Branch of Government the difference between the two bottles, that a young mom may go and heat up the baby formula?

Dr. ALDERSON. Again, Senator, I do not know what the specific bottles that have BPA in them—how they are recommended for use. I can only relate back to when my two children were babies and I know we did not boil hot formula in the bottles.

Senator NELSON. I think back when my two children were young and I did not know up from down.

[Laughter.]

Senator NELSON. All right. Well, let me ask you, Dr. Wind. You are a scientist. Now, one study of your agency that has helped set the foundation for a final determination to deny the petition that infants 1 to 2 years old on average—it came out with a conclusion that those infants 1 to 2 years old mouthed soft plastic toys for 1.9 minutes a day. Does that change your testimony at all about phthalates?

Dr. WIND. No, because that was the very number that we used when we looked at the risk. We developed an acceptable daily intake which is the amount that you can consume for your entire lifetime every day that would result in no health risk. And then we compared the amount of time an infant would mouth these products. We measured how much migrates out of the products, and we did actual calculations where we looked at what, in fact, an infant would consume. And the numbers that we came up with were below the estimated background level that infants would consume from food and other things, and it was way below the acceptable daily intake which already has a safety factor.

Senator NELSON. Just so I understand, then I will stop, Mr. Chairman. So the CPSC has concluded that a child mouthing a flexible plastic toy with phthalates close to 2 minutes a day, that they are not going to have enough of that phthalate to be harmful to the child.

Dr. WIND. Yes, and in fact, the Chronic Hazard Advisory Panel, which consisted of seven independent scientists, recommended to the Commission by the National Academy of Science, concluded that the only children that would be at risk were those that mouthed phthalate-containing toys for more than 75 minutes a day.

Senator NELSON. Thank you, Mr. Chairman.

Senator PRYOR. Thank you.

Let me follow up, if I may. I do not want to pick on Nalgene as a company. It sounds like they are trying to be proactive to try to get ahead of this. So I appreciate that. But just using them as an example, they have announced that they are not going to put BPA in their bottles anymore.

Dr. Alderson, what assurance do we have that whatever chemical goes into the new bottle is safe?

Dr. ALDERSON. If it is a chemical that has previously been approved and is in our regulations as approved, that chemical would have to be used in accordance with those regulations, and that way we would assume it is safe until we get additional information.

If it is a totally new chemical that we have not seen before, it has not been approved for that use, then they would have to get a preclearance approval. They could not start using it until that approval takes place. They would have to go through considerable time and effort to show safety through the regulatory process we have talked about previously in terms of multigeneration studies, chronic studies, et cetera, if the endpoints we see in studies point to that.

Senator PRYOR. So your view is that in order to put any additive there, that additive has to be preapproved by you?

Dr. ALDERSON. That is correct.

Senator PRYOR. Let me ask, if I may, of the CPSC, Dr. Wind. From your earlier testimony in your opening statement, I was not clear on one point. Does the CPSC have a comprehensive list of all products that use phthalates?

Dr. WIND. No. We have concentrated on toys that are intended to be mouthed because our exposure study showed that those were the ones to which kids had the most exposure, and since there was no risk to those, then we did not pursue other toys, although when we were responding to the petition, we did pick up a variety of toys and look at them to see how much phthalate migrated out of them.

Senator PRYOR. All right. For phthalates, is there a level, sort of a magic number, that you consider safe?

Dr. WIND. What we found when we looked at toys was that there was no correlation between the amount of phthalate that was in a toy and the amount that migrated out of it. However, again, I go back to our exposure study, and the levels of phthalates in the toys ranged up to 39 percent, and based upon the exposure time, we did not find that those posed a health risk.

Senator PRYOR. Senator Kerry has joined us. Senator Kerry?

STATEMENT OF HON. JOHN F. KERRY,
U.S. SENATOR FROM MASSACHUSETTS

Senator KERRY. Thank you very much, Mr. Chairman, for a hearing that I think is of incredible importance, and I am very appreciative to you for having it.

I am not entirely sure of where to begin here, but let me get organized and then I will sort of pull that together.

Endocrine disrupters, as we have come to know them, are prevalent in our society, and I know that we are looking at two of those specifically here, phthalates and bisphenol A. There is a lot of scientific evidence showing that at low exposure levels, these two chemicals, which we know are contained in everything from baby bottles to IV tubes, can have real and significant impacts on child development and hormone function. Phthalates are very common in personal care products.

And we seem to have a different attitude in our country than the Europeans do about these kinds of products. I think in Europe they have a burden of proof on the industry to prove that something does not harm them. Here in America, for regrettable reasons, we

have a burden of proof on the individual to prove that it does harm them. Our TSCA, which we passed in 1972, really gets it backward in my judgment. And I am very concerned, Dr. Alderson, Dr. Wind, that the agencies that are supposed to be protecting consumers are simply not doing it.

Americans use 12 personal care products every single day. They contain 126 unique ingredients. And many people assume that simply because the Government requires tough testing for drugs, that the same is true for these personal care products. But it is not true, is it?

Dr. ALDERSON. No, sir.

Senator KERRY. They do not get any kind of real scrutiny, and the reality is that outside of drugs and pesticides, the chemicals used to manufacture many of the products that we use every day, cosmetics, personal care, cleaning agents, are actually never tested to find out if they are harmful. Is that not correct?

Dr. ALDERSON. As it relates to personal care items, particularly cosmetics, the industry conducts an extensive evaluation of their products, but FDA does not get to see any of that information.

Senator KERRY. Just the way that Chevrolet years ago did evaluations on the Corvair. Correct? And many other instances like pajamas that used to catch on fire and beds that kids fall through and hang themselves in. Correct?

So somebody is supposed to stand up here and sort of protect people a little bit. In my judgment, the FDA could hardly be doing less. They do not require studies or testing for a cosmetic product that is put on the shelves of the pharmacy or grocery store. I am told that some hair straighteners use estrogen. Are you aware of that?

Dr. ALDERSON. No, sir.

Senator KERRY. Are you aware of that, Dr. Wind?

Dr. WIND. That is not something in our jurisdiction, so no.

Senator KERRY. Even if it were not in your jurisdiction, you are not aware of it.

Dr. WIND. No.

Senator KERRY. And estrogen can, in fact, have carcinogenic impact when it is used in a certain quantity above normal levels. Would it concern you to know that young women are using estrogen in hair products conceivably to straighten their hair and that that may, in fact, have an impact?

Dr. ALDERSON. Without question we would want to know that, sir.

Senator KERRY. Well, it is in the public domain. It seems to me the FDA is putting its faith in an industry to self-police through a panel called the Cosmetic Ingredient Review. Surprise, surprise. The industry funded the panel of scientists and they have reviewed only 11 percent of the more than 10,000 ingredients contained in cosmetics.

The reality is that these pose risks to health. Dozens of studies in recent years led to the announcement in mid-April from the National Toxicology Program of the National Institutes of Health that there is "some concern about neural and behavioral effects of BPA on fetuses, infants, and children." In response to this, Senator

Schumer and I introduced the BPA-Free Kids Act of 2008, which prohibits the use.

But again, we have been slow to take this up. In fact, the response from the recent study of the National Toxicology Program has simply promised more studies, not any concrete action to reduce exposure.

The media has reported that the Federal Government's reluctance to regulate these chemicals is based on the reliance of biased studies from the chemical industry itself.

Now, I have to tell you if that is true, if it is not being done independently or by yourselves, but by an industry study, does that not cast amazing doubt on the ability of the regulatory system to actually protect the public?

Dr. ALDERSON. Senator, at FDA all of our products that we approve are based on data that are prepared and conducted in studies by that particular manufacturer.

Senator KERRY. But does that not bother you? That is my point. You do not seem to see the connection here.

You know, my wife and I did a book. I am not here to hawk a book, but we wrote a book. A chapter in it is on this topic. Let me just read something about baby food. "Chemicals that go into the manufacture of other products intended for young children. Polyvinyl chloride softens because of the existence of phthalates. It is still used in the manufacture of children's toys, bath books, rattles, beach balls, plastic raincoats, boots, even teething rings, and it can be absorbed from those products during use into a young child's body."

"The fact is that a biomonitoring study coordinated by EWG, the Environmental Working Group, tested the umbilical cord blood from 10 babies who have been born in the United States in August and September of 2004. These newborns were found to have absorbed in the womb a combined total of 413 chemicals. At birth, each child carried an average body burden of 200 chemicals, and those chemicals included pesticides, flame retardants, and other persistent organic compounds or byproducts from burning gasoline and garbage."

"The EWG also tested the breast milk of 29 first-time mothers from across the United States for the presence of components of chemical flame retardants, TVs, foam furniture, all of which can cause thyroid toxicity, and some of which have been banned in Europe. And the results were very sobering. The breast milk of each new mother tested positive for components of flame retardants. The average level of brominated fire retardants in the milk samples was 75 times higher than the average for women who had been tested in Europe and were at levels associated with toxic effects in studies on lab animals."

You can go on and on about what is happening with phthalates themselves. There were some doctors who were doing an analysis. I think it was in Pittsburgh at the university. They were trying to figure out what the impact was of plasticizers, phthalates on creation of cancer, and before they even put the cancerous carcinogen into their experiment, they found that their base product had already turned cancerous. And they could not figure out why.

So they started doing reverse analysis to figure out what had happened, and then they got to the point where they actually made telephone calls to the makers of the plastic tubes to find out what the ingredients were and, indeed, found that the phthalates within the tubes themselves were the only rationale for what had created the carcinogenic transformation.

Do you read these studies? Do they not concern you?

Dr. ALDERSON. Sir, we have read all the studies you are talking about.

Senator KERRY. Well, why do you not ban phthalates? There is a movement in California to ban them now. There is a movement in Europe, other places. There is a lot of study in rats and others. Are you familiar with those studies?

Dr. ALDERSON. I personally am not, but I am sure the scientists at FDA who review these materials every day are.

Senator KERRY. Well, does the Commission not talk about this? Do you Commissioners not talk about this?

Dr. ALDERSON. We talk about these issues on a regular basis, Senator.

Senator KERRY. A team at Boston Tufts University, led by Professor Soto, studied the effects of phthalate exposure in rats. They exposed pregnant rats to bisphenol A, BPA, chemical, and the levels to which the rats were exposed mirrored levels that humans encounter daily. The results: by the time they reached puberty, rats that had received even the lowest doses of BPA had four times more precancerous growths in breast tissue than those that had not been exposed.

You think it is OK for people to go ahead and use this stuff? I mean, does this not concern you?

Dr. ALDERSON. Senator, it does concern us.

Senator KERRY. Well, how much does it concern you? Enough that all you do is just rely on a study that comes from the industry itself? You should go to their website today and read what they say about phthalates. Completely contrary to what is out there in scientific journals. It is a disgrace. And it obviously does not concern you enough to do something about it.

There are thousands upon thousands of chemicals; 80,000 chemicals are out there in the marketplace today. Something like less than 6,000 have been properly vetted and tested. And we are still living with the residue of the Toxic Control Substances Act that was written by the industry with the burden of proof on our citizens to prove harm done, not on people to prove that it will not be done.

And I tell you—I mean, I could go on and on. I have used my time here, and it is not appropriate to abuse it. But I just think the job is not being done, sir, I have to tell you. And I do not think the American public is being adequately protected, and I think we are going to have to find—this law has got to be rewritten and we have got to start to do what we are supposed to do, not what the industry always asks us to do.

Do you have any response? None. You think everything is OK?

Dr. ALDERSON. Senator, as the studies become available to us, we at FDA——

Senator KERRY. Studies from whom become available to you?

Dr. ALDERSON. Whoever. If they have been published——

Senator KERRY. The only studies you are getting right now—have you asked for studies from independent sources?

Dr. ALDERSON. We do not normally ask for independent studies.

Senator KERRY. Then you do not protect the American people if you do not ask for them, if you do not look beyond what is handed to you.

Thank you, Mr. Chairman.

Senator PRYOR. Thank you.

That will be all for this panel here. I want to thank you all for being here and providing your testimony. And just to let you all know, it is very possible that Senators will have written questions, and they will submit those for the record and we will keep the record open for 2 weeks to allow Senators to submit their questions and you all to get your answers back.

Now I would like to introduce the third panel. You all just come on up and grab a microphone and grab your seats.

First is going to be Dr. John Peterson Myers, CEO and Chief Scientist, Environmental Health Sciences. Next will be Ms. Elizabeth Hitchcock, Public Health Advocate for U.S. PIRG, and third will be Dr. Steve Hentges, Executive Director, Polycarbonate/BPA Global Group, American Chemistry Council.

So as you all are getting situated and finding your seats, I want to welcome all of you to the subcommittee. And Dr. Myers?

STATEMENT OF JOHN PETERSON MYERS, PH.D., CEO AND CHIEF SCIENTIST, ENVIRONMENTAL HEALTH SCIENCES

Dr. MYERS. Mr. Chairman, distinguished Members of the Committee, my name is Pete Myers. I am the Chief Scientist of Environmental Health Sciences, a not-for-profit scientific organization based in Charlottesville, Virginia. It is an honor to be here today to participate in this discussion.

I am going to focus most of my comments on some of the issues that were raised by your questions earlier, specifically this whole high-dose versus low-dose issue because it turns out that the structure, the basic way that the FDA, the EPA, and the CPSC have gone about asking scientific questions to respond to Senator Kerry's concerns are based upon 16th century science, not upon 21st century medicine. And that has left us blind to exactly the types of effects that bisphenol A and the phthalates now are shown to have caused in a wide array of experiments. I will get to that.

I first want to begin with a couple of preliminary comments. As Senator Kerry knows, over 10 years ago, I actually co-authored a book about endocrine disruption that brought this issue to the attention of the American public and policymakers for the first time. Even then, over 10 years ago, there were hints of risks from bisphenol A and phthalates.

As I look at the last 10 years, the book's most important effect actually was to stimulate Federal investments in medical and scientific research on endocrine disruption, and today, 10 years later, we are living midstream in a scientific revolution that has resulted from those investments, and it is truly quite amazing. It is changing the framework we use to think about how contaminants can be

toxic because the old toxicology focused on overt damage, overt toxicity. Are mutations caused? Is there overt liver toxicity, et cetera?

This new toxicology instead looks at molecular genetics, and it acknowledges that our genes are actually being turned on and off trillions of times a second every day of our life, every second of our life, and things like phthalates and bisphenol A affect that process of turning genes on and off.

The FDA and the EPA and the CDC—their science currently ignores molecular genetics. It looks at old-style toxicology, the consequences of high doses, but we are learning that this new toxicology, toxicology that builds upon the last several decades of molecular genetic research, is really revealing that the changes in gene expression that can be induced through low-level exposures in the womb can lead the developing organism along a path that it never would have followed and induce diseases in adulthood that are actually traced to what are called epigenetic changes caused by low-level exposures in the womb. That is the central issue here. We have got to move from 16th century science to 21st century science.

If you leave this room with just one new piece of information, here it is. Numerous animal studies published in the peer-reviewed literature show that the average person in America today has levels of bisphenol A in their blood that are higher than those sufficient to cause harm in animals. This is a not a case of high-dose experiments being extrapolated to the consequences of low-dose exposure. These are experiments using low doses asking what happens when animals are exposed to the levels that people experience. And crucially, the mechanisms of action of these low-dose exposures are identical. They are exactly the same in animals as they are in people. So the results of those experiments are highly relevant to predicting human effects.

Last and again about bisphenol A, I want you to focus on another fact that has been published in the peer-reviewed literature. Of the studies of bisphenol A that were funded by Government sources, including the National Institutes of Health, over 90 percent of them find adverse effects on animals. In contrast, none of the studies funded by industry report adverse effects. This is the same pattern, the very same pattern, you will find with industry-funded studies of the effects of lead, pharmaceuticals, other chemicals, and tobacco.

Now, some of you will recall the testimony in 1994 before Congress of the seven heads of tobacco companies who swore that there was no link between cigarette smoking and cancer. As you listen to industry interpretation of the data on bisphenol A and phthalates, I would encourage you to think about that.

I would also encourage you to take a look at this new book by Dr. David Michaels of George Washington University. It is called *Doubt is Their Product.* It describes in detail how industry trade groups manipulate science to forestall action, regulatory action. Every delay keeps sales going and revenue flowing.

But back to this larger issue of the contrast between high doses and low doses. I want to give you one specific example, which really brings this home, and it is actually about a drug called tamoxifen. Now, tamoxifen, as many of you know, is used to fight breast cancer. At high levels, it suppresses the rate of growth of a

breast tumor. It is very good at parts per million, parts per thousand levels, and physicians take great advantage of that. But if you go down the dose-response curve, to a level that is literally a million times beneath the level where it is effective as a drug stopping breast cancer, it stimulates proliferation of the breast tumor. It is an estrogen at that level. The high-dose experiments that our regulatory agencies have depended upon to anticipate low-dose effects do not work when you are dealing with compounds that behave like hormones. This is a widely accepted fact in medical endocrinology. It is just not challenging at all.

The question is, when are we going to bring the toxicological community into the 21st century of science?

Thank you.

[The prepared statement of Dr. Myers follows:]

PREPARED STATEMENT OF JOHN PETERSON MYERS, PH.D., CEO AND CHIEF SCIENTIST, ENVIRONMENTAL HEALTH SCIENCES

Base Health Standards on 21st Century Medical Science, Not 16th Century Dogma

Large scientific literatures of peer-reviewed publications now plausibly link bisphenol A (BPA) and several phthalates to an array of adverse health outcomes.

For bisphenol A these include prostate and breast cancer, loss of fertility (including via polycystic ovaries and uterine fibroids, as well as reduced sperm count and spontaneous miscarriage) and impaired neurological development. Numerous studies show that many of these effects can be caused in laboratory animals at levels beneath the average concentration found in American serum today.[1]

For phthalates these include abnormalities in the male reproductive tract (including undescended testes, hypospadias and reduced sperm count) as well as heightened sensitivity and reactivity of the immune system, which may lead to hyperallergic reactions and asthma.

The strength of the evidence varies for each of these potential effects, for both phthalates and BPA. The human data on phthalates are stronger; indeed for BPA there are almost no epidemiological studies. But the evidence from animal experiments on BPA, especially at very low doses within the range of common human exposure, is much more extensive than with phthalates. And the mechanism of action of BPA in humans is the same as the mechanism of action in animals. Hence the animal findings are highly relevant to predicting human health impacts.

Despite this evidence, both BPA and phthalates are in widespread, indeed ubiquitous use in commerce today. Virtually all Americans carry measurable levels in their fluids and tissues. None of the relevant Federal agencies have taken action to reduce exposures.

Why?

The scientific basis of regulatory toxicology, as it is applied today by Federal regulators, rests upon an assumption derived from 16th Century dogma. That assumption, never tested in standard procedures to establish acceptable exposure limits, conflicts directly with 21st Century medical science.

The assumption is that experiments with high doses will reveal the effects of low doses. It is based upon the 16th Century observation by Paracelsus that "All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy."[2] This has been paraphrased to become "the dose makes the poison."

The assumption is directly contradicted by decades of research in the medical science of endocrinology showing that hormonally-active compounds have complicated dose-response curves in which low dose exposures can cause effects unpredictable from high dose experiments. BPA and phthalates are both hormonally-active compounds, called endocrine disrupters (EDCs), and peer-reviewed research has reported these complicated dose-response curves for both substances. Nevertheless, the FDA and EPA continue to depend upon this flawed assumption, which has been repeatedly invalidated in careful scientific studies, in these agencies' development of public health standards for, and regulation of, exposures to EDCs. This misled policy is disastrous, as it will lead to many lost opportunities for improving public health that will have implications for decades, as recent research shows long-term

detrimental effects not only on exposed individuals, but even subsequent generations.

Biomonitoring studies conducted by the CDC and others document that wherever samples have been analyzed, people are contaminated with many industrial chemicals, including BPA and phthalates. Of particular concern are the numbers and concentrations of chemicals found in human amniotic fluid, fetal blood, and breast milk, rendering it impossible for a child to be born or to be breast-fed without developmental exposure.

Many of these chemicals are known to interfere with the action of hormones in experimental systems, hormones that are essential for healthy development. With a mandate from Congress, for the last decade the U.S. EPA has been designing regulatory tools to screen and test for contaminants with endocrine effects.[3] To date, this process has failed to fully integrate basic endocrinological principles in its decision-making and instead is relying upon toxicological methods that are inappropriate for EDCs.[4] This led to a significant blind-spot in regulatory standard setting.

Chemical monitoring by the CDC, carefully structured to obtain statistically representative estimates of Americans' exposures, typically reveals median serum or urine concentrations well below those produced by dosing regimens in animal experiments used for regulatory toxicology. Those regimens use high doses under the assumption that the effects of high doses can be used to predict low dose impacts. In fact, the estimates of safe daily human exposure doses for chemicals derived from these procedures are never directly tested, even in laboratory animals. Yet increasingly, epidemiological analyses of biomonitoring data showing associations, sometimes striking, between the low concentrations of chemicals measured in the general public and adverse health conditions. Examples include phthalates and sperm defects,[5] reproductive tract abnormalities,[6] and obesity;[7] pesticides and sperm count;[8] perchlorate[9] or PCBs[10,11,12] and thyroid function; and persistent organic pollutants and type 2 diabetes[13] and insulin resistance.[14]

These associations should not arise if the safety levels established by high-dose testing are accurate. Several factors could be contributing to this apparent discrepancy between prediction and observation. One is that epidemiological associations do not reflect causality. A second is that the estimate for safety has been based upon an insensitive endpoint. A third is the potential for additive or synergistic effects of mixtures. I will focus here on a fourth, because it challenges the core assumption of regulation toxicology, that high-dose testing is sufficient to predict low-dose effects. A huge experimental literature amassed over decades of mechanistic research in endocrinology demonstrates that this assumption is fundamentally flawed and is highly vulnerable to missing important low-dose adverse effects.

Paracelsus's observation, above, reflects an intuitively logical concept that the higher the exposure, the greater the impact. Testing with high doses, in this view, should reveal any hazards and do so more efficiently than testing with low doses, because the effects will be stronger and easier to detect. This centuries-old paradigm remains the central tenet of modern regulatory toxicological approaches to studying the health effects of chemicals.

Paracelsus' logic holds if and only if chemicals' effects faithfully follow a monotonic dose-response curve. When toxicologists began to focus on potential health effects of chemicals classified as endocrine disruptors, endocrinologists began to raise questions about the appropriateness of assuming monotonicity in toxicological studies of hormonally-active chemicals used in common household products.

Monotonic vs. non-monotonic dose-response curves.

Non-monotonic curves are often described as 'U shaped' or 'inverted-U' shaped.' Monotonic and non-monotonic refer to changes in the slope of the curve describing dose and response. Monotonic curves may be linear or non-linear, but the slope never reverses from positive to negative or vice-versa. Non-monotonic curves change sign, from positive to negative or vice-versa.

The basis for this concern is that non-monotonicity is a general characteristic of hormones. This issue is so central to hormone action that it is a critical component of determining the dose required for hormonally active drugs; an example is Lupron used to treat reproductive disorders in women and prostate cancer in men, since low doses stimulate while high doses inhibit tumor growth.

These non-monotonic curves can result from multiple mechanisms, which have been studied by endocrinologists, pharmacologists and neurobiologists for decades. Hormones and hormone-mimicking chemicals act through receptors in target cells. Very low doses can stimulate the production of more receptors (called receptor up-regulation), resulting in an increase in responses, while higher doses (within the typical toxicological range of testing) can inhibit receptors (called receptor down-regulation), resulting in a decrease in responses. The consequence for gene activity, which is regulated by hormone-mimicking chemicals binding to receptors, is that very low doses of these chemicals (in the case of a positively-regulated gene) can up-regulate gene expression, while at higher doses the same chemicals down-regulate gene expression.[1,15] In addition, myriad hormonal feedback mechanisms between the brain, pituitary gland and hormone producing organs (thyroid gland, adrenal glands, ovaries, testes) contribute to the presence of non-monotonic dose-response curves. Equally important, at high doses, hormones and hormone-mimicking chemicals can bind to receptors for other hormones (*e.g.,* estrogens can interact with androgen and thyroid receptors), producing entirely different effects from those seen at low doses where only binding to estrogen receptors occurs. Also, there is non-specific (non-receptor mediated) toxicity that can occur at high but not low doses. The consequence is that there are qualitative as well as quantitative differences in the effects of high and very low doses of endocrine disrupting chemicals.

Notably, EDCs may also act by mechanisms that do not require direct mediation of classical hormone receptors. For example, they also exert actions upon synthesis or function of enzymes that may be responsible for the synthesis or degradation of hormones; on factors that interact or regulate receptors such as coregulatory factors; and in the case of neurological actions, through neurotransmitter receptors.[16] This concept is important because each of these mechanisms may have a unique dose-response sensitivity to an EDC, adding to the complexity of the overall shape of the dose-response curve.

A recently published example of a non-monotonic response in an animal model, with high biomedical relevance to humans, involves the estrogenic drug diethylstilbestrol (DES), once widely used to treat difficult pregnancies but removed from the market in 1971 because it was found to cause a rare cancer in young adult women who had received fetal exposure. Research has established the BPA is structurally and functionally very similar to DES.

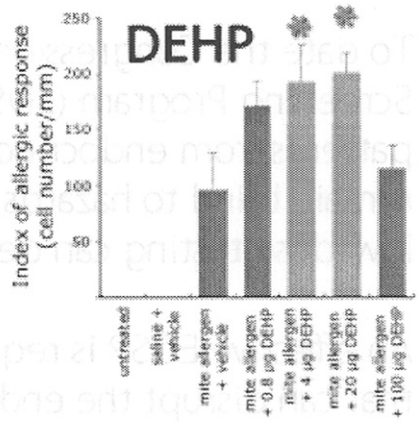
Mice exposed perinatally to relatively high doses of DES (1000 μg/kg/day) had reduced body weight in adulthood, but a much lower dose (1 μg/kg/day) caused adult obesity (figure to right).[17,18]

The mouse on the right received the extremely low dose compared to the control on the left. The researchers reported no difference between control and experimental animals in either calories consumed or energy expended.

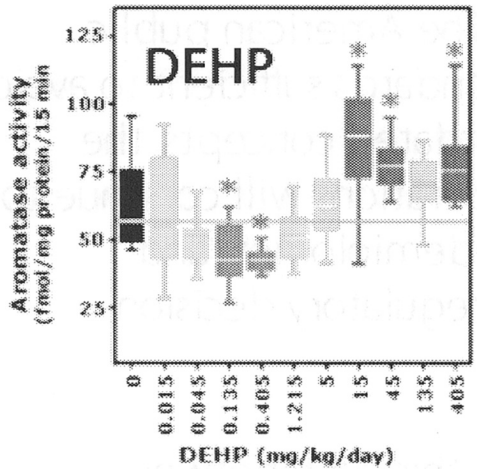
A similar non-monotonic response has been observed for DES effects on the developing prostate in mice.[19,20,21] A traditional high-dose testing regimen with DES would never have revealed these low-dose effects.

Just as with DES, industrial chemicals that interfere with hormone signaling cannot be expected to follow monotonic dose-response rules. Non-monotonicity has been reported repeatedly for adverse effects with a number of endocrine disrupting compounds, including the bisphenol A, the phthalate DEHP, the pesticides, dieldrin, endosulfan and hexachlorobenzene, the pesticide metabolite DDE, and arochlor 1242, a PCB mixture.[22]

Effects include strong exacerbation of allergic reactions following exposure to DEHP at a concentration one thousand-fold beneath the current safety standard, which is based on high dose liver toxicity (figure below)[23] and increased allergic responses caused by picomolar level exposures (parts per trillion) to several persistent organic pollutants.[24] Cells exposed to concentrations of these pollutants a million times higher than the level producing the maximum response showed no effect.



An experiment (figure below) with rats that involved administration of DEHP was explicitly designed to test the adequacy of high-dose testing.[25] It found that a high dose increased estrogen synthesizing (aromatase) enzyme activity in the brains of neonatal male rats; a dose 100-fold lower appeared to be the "no effect dose", which is used to estimate the dose deemed safe for human exposure (this enzyme is involved in determining sex differences in brain function).



In the experiment above, only because the scientists broke with tradition and also tested lower doses did they find significant down-regulation of aromatase at a dose 37-times lower than the putative no effect dose, an effect opposite to and unpredicted from only testing very high doses.

Other experiments have documented non-monotonicity in rat pituitary cells exposed to pico- through micro-molar levels (parts per trillion to parts per billion) of BPA.[26,27] Acting through a relatively recently discovered estrogen receptor on the surface of the cell membrane, very low picomolar concentrations of the contaminant increased calcium influx and activation of enzyme cascades that dramatically amplify a very low-dose signal into a large cellular response. The dose-response curve followed a strongly non-monotonic, 'inverted-U' shape, with the strongest response at low nanomolar levels. The bioactive concentrations of bisphenol A in these experiments were actually far below the range found ubiquitously in human blood and urine. Another endpoint that follows a non-monotonic pattern is human prostate cancer cell proliferation in response to bisphenol A,[28] with the peak response occurring exactly within the range of exposure of men to bisphenol A based on biomonitoring studies.[1,29]

Research over the past 20 years has identified large numbers of endocrine disrupting contaminants that are capable of mimicking or disrupting hormone function. Biomonitoring studies have established that many are widespread contaminants in people. Yet regulatory toxicology as it has been practiced for decades, and as it has been used to set public health exposure standards, ignores non-monotonicity despite the fact that, similar to hormones, all should be expected to display non-monotonic dose-response patterns.

To date the Congressionally-mandated effort by the EPA, called the Endocrine Disruptor Screening Program (EDSP), has not acknowledged these common, indeed standard patterns from endocrinology, and hence it is on course to select methodologies that will remain blind to hazards posed by low doses that lead to adverse effects that only direct low-dose testing can detect.

An effective EDSP is required to protect Americans from exposure to industrial chemicals that can disrupt the endocrine system, which must function properly for normal development to occur as well as for normal adult function. Significant exposure to these chemicals is through the food supply, which is the domain of the FDA, but exposure also occurs through drinking water and air, the domain of the EPA. The American public depends upon these regulatory agencies to set public health standards sufficient to avoid harmful exposures. But until the FDA and EPA move beyond outdated concepts, the public health standards that emerge from their regulatory deliberations will continue to produce a disconnect between what human bio-

monitoring, epidemiological and mechanistic endocrine studies in animals reveal and what their regulatory decisionmakers allow.

Were the health implications of these decisions inconsequential, this clash between toxicology and endocrinology would appropriately remain buried in academia. But the range of health conditions now plausibly linked to endocrine-disrupting contaminants—including prostate cancer, breast cancer, attention deficit hyperactivity disorder, infertility (including both male and female reproductive problems), miscarriage, and most recently, hyper-allergic diseases, obesity and type 2 diabetes—makes it imperative that the clash between basic endocrinologists and regulatory toxicologists becomes public and addressed by regulatory agencies. These diseases are major contributors to American's steadily increasing disease burden and to the escalating cost of health care. Extensive, careful and replicable animal research suggests that numerous industrial chemicals to which people are exposed every day, but which have not been adequately studied for health effects in humans, may be significant contributors to these adverse health trends.

As endocrine and reproductive systems are highly conserved between animals and humans, there is no doubt that basic research results on EDCs are directly applicable to human health. Modernizing relevant health standards by incorporating endocrinological principles could help reduce a significant portion of the human disease burden, but this will require regulatory decisionmakers to begin asking scientifically appropriate questions. The soaring health care crisis in the U.S. demands that the regulatory apparatus of Federal Government get this right. Blind obedience to 16th century dogma will not solve the problem.

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Senator KLOBUCHAR [presiding]. Thank you, Dr. Myers.
Ms. Hitchcock?

STATEMENT OF ELIZABETH HITCHCOCK, PUBLIC HEALTH ADVOCATE, U.S. PUBLIC INTEREST RESEARCH GROUP

Ms. HITCHCOCK. Good morning. Members of the Committee, I am Liz Hitchcock, Public Health Advocate for the U.S. Public Interest Research Group. I have submitted longer written testimony for the record, but I would like to cover three important points in this hearing.

One, the hazards of bisphenol A and phthalates are well documented and pose a special danger to children.

Two, other countries, a number of states, and retailers are acting in the absence of Federal action on these chemicals.

Three, the Federal Government should regulate these and other toxic chemicals to protect our children's health.

To begin, we would like to commend the Committee for its efforts to improve U.S. product safety, including the recent Senate passage of the CPSC Reform Act. When reconciled with the House bill, it will take long overdue steps forward in protecting America's children from unsafe products. We encourage the conference committee to take the strongest parts of each bill. In particular, we believe that the Senate bill's provisions addressing the toxic hazards of lead and phthalates in children's products are important steps to take preventable hazards out of the marketplace.

First, the hazards of bisphenol A and phthalates are well documented, as Dr. Myers and others have told you in their testimony. For 22 years, U.S. PIRG *Trouble In Toyland* safety reports have identified hazards to a population that is notorious for putting everything in their mouths, small children. We have increased our focus in the last 10 years on chronic hazards posed by unnecessary exposure to lead, phthalates, and chemicals known to be toxic.

In 1998, we joined a number of public interest groups in petitioning the CPSC to ban polyvinyl chloride in all toys intended for children under the age of 5 because of the potential health hazards posed by phthalates. In 2003, the CPSC denied our petition.

Phthalates are widely used and can be found in many children's products, including teethers, bath books, raincoats, and as Senator Klobuchar pointed out, rubber duckies.

Last year, U.S. PIRG's partner organization, Environment California, tested five of the most popular baby bottle brands on the market. Our researchers found that the bottles tested from all five brands leached bisphenol A at levels found to cause harm in numerous laboratory studies. Scientists have linked very low doses of bisphenol A to cancers, to impaired immune function, to the early onset of puberty, obesity, diabetes, and hyperactivity, among other problems.

Phthalates have been linked to a number of serious health impacts, including reproductive defects, birth deformities, liver and thyroid damage, neurological impacts, and even cancer.

In April, the National Toxicology Program at NIH finally acknowledged health concerns about children's exposure to BPA.

Given the significant health concerns associated with both bisphenol A and with phthalates, taking a precautionary approach

toward the use of these chemicals just makes sense. In other words, if there is evidence that these chemicals cause harm and if we have safer alternatives with which to replace them, then why would we not use precaution and restrict their use?

Second, other countries and a number of States and some manufacturers are leading the way in taking action on these chemicals. For example, the European Union has had a policy restricting the use of phthalates since 1999. At least 14 countries have also restricted the use of phthalates to protect children's health. In the United States, only California and Washington State have enacted phthalate legislation. A Vermont bill is on the Governor's desk right now. But at least a dozen States have either introduced or are considering introducing legislation to restrict phthalate use.

In the private sector, several leading manufacturers of toys and baby products in the U.S. have stopped using phthalates over the last few years. In addition, Wal-Mart and Toys "R" Us announced early this year that they will begin phasing out children's toys containing the chemical in the coming months.

Last month, the Canadian Government declared bisphenol A toxic under Canadian law, triggering a ban on baby bottles with that chemical. There are current efforts in five State legislatures to restrict uses of BPA. Senator Chuck Schumer has introduced S. 2928 banning BPA in all products intended for infants and children up age 7, a bill that U.S. PIRG supports.

Consumers cannot be expected to do it alone and cannot expect all industry and retailers to take the right voluntary steps. The Federal Government should regulate these and other toxic chemicals to protect our children's health.

First, the Federal Government should take action based on the overwhelming weight of evidence showing that chemicals like phthalates and bisphenol A may harm human health.

U.S. chemicals policy should be reformed to require manufacturers to provide all hazard and health impact information to the Federal Government so we can begin to assess the thousands of chemicals currently on the market for which we have little or inadequate data.

And finally, the conference committee and the Congress should pass a final version of the CPSC reform bill that includes the Feinstein Amendment banning phthalates in children's products. The amendment will serve to significantly curb children's routes of exposure to these reproductive toxicants.

We commend the Committee for conducting this important hearing and we hope that you find our comments helpful. We would be happy to discuss other possible actions under the Committee's jurisdiction to protect consumers from chronic and developmental hazards from unnecessary exposure to toxic chemicals in consumer products.

Thank you.

[The prepared statement of Ms. Hitchcock follows:]

PREPARED STATEMENT OF ELIZABETH HITCHCOCK, PUBLIC HEALTH ADVOCATE, U.S. PUBLIC INTEREST RESEARCH GROUP

Chairman Pryor, Senator Sununu, Members of the Committee: I am Elizabeth Hitchcock, Public Health Advocate for the U.S. Public Interest Research Group. U.S.

PIRG is the federation of state PIRGs, which are non-profit, non-partisan public interest advocacy organizations with one million members across the country.

We are pleased to present our views at this Oversight Hearing on Bisphenol-A, Phthalates, Consumer Products and Consumer Health. The state PIRGs have long been concerned with the important issues of toxics in consumer products, and the ability of the Federal Government to protect all of us, but particularly our children, from preventable hazards.

Since 1986, we have conducted toy safety research and education projects to avoid preventable deaths and injuries. While our annual *Trouble In Toyland* toy safety reports [1] have emphasized the hazards posed by choking on small parts, we have expanded the report in the past decade to focus on the chronic hazards posed by unnecessary exposure to lead,[2] phthalates and other chemicals known to be toxic.

Summary

First, Mr. Chairman, we commend you for your efforts to improve U.S. product safety, including the recent Senate passage of your bill, the CPSC Reform Act. When it is reconciled with the House bill, it will take significant and long overdue steps forward in protecting America's children from unsafe products. We encourage the conference committee to take the strongest parts of each bill.

In particular, we believe that the Senate bill's provisions addressing the toxic hazards of lead and phthalates in children's products are important steps to take preventable hazards out of the marketplace.

Recent headlines about the long overdue acknowledgement of the National Toxicology Program of the U.S. National Institutes of Health of health concerns about children's exposure to Bisphenol-A (BPA) have raised concerns among consumers about this and other toxic chemicals.

In general, U.S. PIRG's policy recommendations concerning toxic chemicals like Bisphenol-A and phthalates are that the Federal Government should:

- Phase Out Dangerous Chemicals. The U.S. Environmental Protection Agency should take action based on the overwhelming weight of evidence showing that chemicals like phthalates and bisphenol-A may harm human health.
- The U.S. should phaseout the use of Bisphenol-A, especially in children's products. Due to the possible increased risks to small children and pregnant women, we strongly urge the removal of BPA from all products intended to contact food.
- Reform U.S. Chemicals Policy. Manufacturers should be required to provide all hazard and health impact information to the EPA so the agency can begin to assess the thousands of chemicals currently on the market for which it has little or inadequate data.
- The Consumer Product Safety Commission should protect consumers, for example, by labeling these products with the names of the chemicals they contain to allow parents to choose less toxic products, among other protective actions.
- The conference committee and the Congress should pass a final version of CPSC reform legislation including the Feinstein amendment banning phthalates in children's products (incorporated as Section 40 of H.R. 4040, the CPSC Reform Act, as passed by the Senate).[3]

1. Phthalates Are Ubiquitous With Exposure Linked To Health Effects

Phthalates are a family of chemicals, including diethyl phthalate (DEP), diethylhexyl phthalate (DEHP), dibutyl phthalate (DBP), butyl benzyl phthalate (BBP), diisodecyl phthalate (DIDP), diisononyl phthalate (DINP), di-n-octyl phthalate (DNOP), and many other distinct types. The polyvinyl chloride (PVC) plastic industry uses large amounts of phthalates as additives to improve the flexibility of its products, including home siding, flooring, furniture, food packaging, toys, clothing, car interiors, and medical equipment, including IV bags. In addition, other manufacturers use phthalates in personal care products such as soap, shampoo, deodorant, hand lotion, nail polish, cosmetics, and perfume, as well as industrial products like solvents, lubricants, glue, paint, sealants, insecticides, detergent, and ink.[4]

Phthalates are pervasive in the environment and in human bodies. In 2000, the Centers for Disease Control (CDC) found high levels of phthalates and their transformation products (known as metabolites) in every one of 289 adult Americans tested, including women of childbearing age.[5] Larger CDC studies in 2003 [6] and 2005 [7] again found high levels of phthalates in almost every person tested.

Numerous scientists have documented the potential health effects of exposure to phthalates in the womb or at crucial stages of development, including (but not limited to):

- *Reproductive Defects.* Scientists have demonstrated links between exposure to phthalates in the womb with abnormal genital development in baby boys and disruption in sexual development.[8] In October 2005, an independent panel of scientists convened by the National Institute of Environmental Health Sciences and the National Toxicology Program released its review of one type of phthalate, diethylhexyl phthalate (DEHP). The panel confirmed that DEHP poses a risk to reproductive and developmental health.[9]
- *Premature Delivery.* A study published in November 2003 suggests a link between exposure to phthalates and pre-term birth. The scientists found phthalates and their breakdown products in the blood of newborn infants, with higher levels leading to a higher incidence of premature delivery.[10]
- *Early Onset Puberty.* One study of Puerto Rican girls suggests that phthalates may be playing a role in trends toward earlier sexual maturity.[11] Scientists found that levels of DEHP were seven times higher in girls with premature breast development than levels in normal girls.
- *Lower Sperm Counts.* In 2003, Drs. Susan Duty and Russ Hauser of the Harvard School of Public Health published one of the first studies linking phthalate exposure with harm to human reproductive health.[12] Men who had monobutyl or monobenzyl phthalate in their urine tended to have lower sperm counts, with the highest concentrations leading to the lowest sperm counts.

2. History of Efforts to Ban Phthalates in Children's Toys and Products

In 1998, the state PIRGs and several other environmental and consumer groups petitioned the Consumer Product Safety Commission, asking the agency to ban polyvinyl chloride (PVC) plastic in all toys intended for children under the age of five because of the potential health hazards posed by diisononyl phthalates (DINP). While noting its position that "few if any children are at risk from the chemical,"[13] in December 1998 CPSC asked the toy and baby products industry to remove DINP from soft rattles and teethers. About 90 percent of manufacturers indicated at that time that they had removed or would remove DINP from soft rattles and teethers by early 1999. CPSC staff also asked the industry to find a substitute for phthalates in other products intended for children under 3 years old that are likely to be mouthed or chewed.[14]

CPSC also convened a Chronic Hazard Advisory Panel to examine the existing scientific data concerning the potential risks of phthalates to humans. In June 2001, the panel concluded that while the majority of children would not be adversely affected by diisononyl phthalate, "there may be a DINP risk for any young children who routinely mouth DINP-plasticized toys for seventy-five minutes per day or more."[15]

Unfortunately, in February 2003, CPSC denied the state PIRGs' petition to ban PVC plastic in toys for young children.[16]

Some manufacturers are beginning to label their baby products and toys as "phthalate-free," which should provide parents the information they need to make educated purchasing decisions. The U.S. government, however, does not regulate the "phthalate-free" label or ensure that products labeled "phthalate-free" actually do not contain phthalates. Since the U.S. government has not established any guidelines for what the label means, or established any standards for the phthalate content in children's products, consumers can only assume that it means phthalates are not present in the item.

In 2005, to test the reliability of the "phthalate-free" label, U.S. PIRG commissioned STAT Analysis Corporation in Chicago, Illinois to test eight soft plastic toys labeled as not containing phthalates. Of the eight toys tested, six contained detectable levels of phthalates.[17] Based on these results, we asked the Federal Trade Commission (FTC) to investigate whether manufacturers' use of the "phthalate-free" label constitutes unfair or deceptive marketing practices when the product actually contains phthalates.[18]

With the results of the FTC investigation still pending, we once again commissioned STAT Analysis Corporation in the fall of 2006 to test 10 soft plastic toys labeled as not containing phthalates.[19] Of the 10 toys tested, just two contained detectable levels of phthalates. Some of the items that tested positive for phthalates in the first year did not in the second. While this may be good news for consumers, nothing in U.S. law has changed to hold manufacturers accountable to their "phthalate-free" label or require them to stop using phthalates. Consumers still have no guarantee that the "phthalate-free" products they purchase truly are phthalate-free, as evidenced by our test results.

A number of individual states and other countries have taken action, however, to protect children's health. In 1999, the European Union (EU) imposed temporary re-

strictions on the use of six phthalates in toys and childcare products.[20] This ban became permanent in January 2006. The EU banned three phthalates classified as reproductive toxicants—diethylhexyl phthalate (DEHP), butyl benzyl phthalate (BBP), and dibutyl phthalate (DBP)—in all toys and childcare articles. The EU banned three other phthalates—DINP, diisodecyl phthalate (DIDP) and di-n-octyl phthalate (DNOP)—in toys and childcare articles intended for children under 3 years of age and that can be put in the mouth.[21]

In the past year, California and Washington State have banned phthalates in children's products; Minnesota and Vermont both have bills on their Governor's desk; and Rhode Island, New York and Massachusetts are considering similar measures.

In March 2008, the U.S. Senate overwhelmingly passed the CPSC Reform Act, with an amendment by Senator Feinstein that eliminates phthalates in children's products and child care articles, which will serve to significantly curb children's routes of exposure to these reproductive toxicants. We urge the conferees to retain the phthalate provision, and its state savings clause, in the final bill.

3. Bisphenol-A: Developmental, Neural and Reproductive Toxicant

Scientists have linked very low doses of bisphenol-A to cancers, impaired immune function, early onset of puberty, obesity, diabetes, and hyperactivity, among other problems.

We know that bisphenol-A can leach from plastic containers and cans and into food and beverages, leading to potentially significant human exposures. A recent study released by the U.S. Centers for Disease Control and Prevention (CDC) found that BPA was in the blood of 95 percent of humans they tested. The median level of BPA found in humans is higher than the level that causes adverse effects in animal studies. BPA raises particularly troubling health questions because it can affect the endocrine system, mimicking the effects of estrogen in the body. Experiments in animals and with human cells strongly suggest exposures typical in the U.S. population may increase susceptibility to breast and prostate cancer, reproductive system abnormalities, and, for exposure in the womb and early childhood, a host of developmental problems. Concerns about early life exposures also extend to early onset of puberty in females, potential prostate problems in males, and obesity.

Last year, U.S. PIRG's partner organization, Environment California, tested five of the most popular baby bottle brands on the market (Avent, Dr. Brown's, Evenflo, Gerber, and Playtex) to determine the amount of leaching from each bottle. Our researchers found that the bottles tested from all five brands leached bisphenol-A at levels found to cause harm in numerous laboratory studies.[22]

The current U.S. Environmental Protection Agency daily upper limit for BPA, 50 micrograms per kilogram of body weight, is based on industry-sponsored experiments conducted in the 1980s. Some animal studies show adverse health affects from exposure of only 0.025 micrograms per kilogram of body weight, yet a polycarbonate baby bottle with room temperature water can leach 2 micrograms of BPA per liter. A 3-month-old baby drinking from a polycarbonate bottle may be exposed to as much as 11 micrograms per kilogram of body weight daily.

Aside from polycarbonate plastic bottles, BPA is also a food additive approved by the Food and Drug Administration (FDA), commonly used in the coatings for the inside of food cans. But a recent report by the National Toxicology Program (NTP) questioned previous FDA findings that BPA is safe for such applications. Their report, issued on April 15, 2008, expressed "some concern" based on animal studies that BPA might affect the neurological systems and behavior of infants and children. Among its conclusions, the NTP report states that, "the possibility that human development may be altered by bisphenol-A at current exposure levels cannot be dismissed."

Independent Science Shows Harmful Effects from BPA, while Industry Science Shows None

A recently-published review of scientific studies shows that, in the last 7 years (through November 2005), 151 studies on the low-dose effects of BPA have been published.[23] None of the 12 studies funded by the chemical industry reported adverse effects at low levels, whereas 128 of 139 government-funded studies found effects. These many studies were conducted in academic laboratories in the U.S. and abroad. Even the 12 industry-funded studies have flaws, however. Of the industry studies, two had its positive control fail—an indication that the entire experiment had failed, not that BPA had not caused an effect.

Another industry study concluded BPA caused no effect, but an independent analysis of the experiment's data by scientists convened by the National Toxicology Program of the U.S. Department of Health & Human Services concluded that in fact there was an effect. Industry scientists had misreported their own results.

The chemical industry relies on an incomplete review of scientific studies by an effort funded by the American Plastics Council at the Harvard Center for Risk Analysis. The panel funded by the American Plastics Council only considered 19 studies in concluding in 2004 that the weight of the evidence for low-dose effects of BPA was weak.[24] As of November 2005, there were 151 published studies on the low-dose effects of BPA.

The last U.S. EPA risk assessment for BPA was based on research conducted in the 1980s and did not consider that BPA was a chemical estrogen. The most recent risk assessment of BPA was based on a comprehensive review of the scientific literature conducted in 1998 by the European Union, with some selected articles added through 2001, at which time few of the current 151 low-dose BPA studies had been published. The most recent review of scientific studies shows effects from exposure to BPA at levels significantly below the current "safe exposure" level established by the U.S. based on experiments conducted prior to 1988.

4. History of Efforts to Regulate Bisphenol-A

In April 2008, the National Toxicology Program of the U.S. National Institutes of Health finally acknowledged health concerns about children's exposure to BPA. Unfortunately, it is unclear whether this determination will lead to any Federal policy changes to protect children from BPA. On April 18th, the Canadian Government declared BPA "toxic" under Canadian Law, triggering a ban on BPA baby bottles in Canada. There are current efforts in state legislatures in California, Massachusetts, Illinois, New York and Rhode Island to restrict uses of the chemical. On April 29, Senator Chuck Schumer introduced S. 2928 banning BPA in all products intended for infants and children up to age 7. Senators Boxer, Clinton, Durbin, Feinstein, Kerry and Menendez are co-sponsors of the bill, which U.S. PIRG supports. The U.S. Food and Drug Administration announced it would review its regulatory policy on BPA. The FDA's reliance on two industry studies finding BPA safe, despite over 100 independent scientific studies linking the chemical to an array of illnesses, including breast and prostate cancer and obesity, is the subject of a Congressional investigation headed by Chairman John Dingell of the House Energy and Commerce Committee.

In addition, some manufacturers and retailers are taking action on the chemical. Playtex Infant Care announced it will stop selling products made with BPA by the end of the year and will give one million free samples of new BPA-free products to potential customers. Wal-Mart and CVS announced they are phasing out BPA baby bottles in U.S. stores. Nalgene announced it would no longer use plastic made with BPA in its water bottles.

5. U.S. PIRG's Policy Recommendations

Consumers cannot be expected to do it alone—as the thousands of harmful and untested chemicals currently on the market pose a super-human challenge to completely avoid exposure. The U.S. Government must act in a manner that assists parents, and ensure that products on the market are not potentially harmful for children.

A. Phase Out Dangerous Chemicals. The U.S. Environmental Protection Agency should take action based on the overwhelming weight of evidence showing that chemicals like phthalates and bisphenol-A may harm human health. The United States should phaseout the use of these chemicals—especially in children's products. Until the U.S. Government acts, state governments should continue to fill the regulatory gap and support policies to phaseout these chemicals as well. CPSC should ban the use of phthalates in all toys and products for children 5 years old and under, and the U.S. should phaseout the use of Bisphenol-A, especially in children's products. The Federal Government should study the health effects of BPA exposure in all age groups and pregnant women, and should focus on the products that have the greatest potential for causing human harm. Due to the possible increased risks to small children and pregnant women, we strongly urge the removal of BPA from all products intended to contact food.

B. Reform U.S. Chemicals Policy. Currently, manufacturers can put chemicals on the market without proving that they are safe. Manufacturers should be required to provide all hazard and health impact information to the EPA so the agency can begin to assess the thousands of chemicals currently on the market for which it has little or inadequate data. Next, manufacturers of chemicals should be required to conduct an alternatives analysis to determine if they are really using the least hazardous chemical for each application. Finally, EPA must have the authority to ban or restrict the use of a chemical if it can harm human health.

C. Consumer Product Safety Commission Should Protect Consumers. The Consumer Product Safety Commission (CPSC) has an obligation to protect consumers from dangerous products. The CPSC should first label these products with the names of the chemicals they contain to allow parents to choose less toxic products. Second, the CPSC should take the precautionary approach and require manufacturers to remove chemicals that may pose a particular threat to fetuses, infants and children, particularly when the chemical is not necessary for the product to function according to design. In addition, CPSC and the Federal Trade Commission should look into manufacturers' use of the "phthalate-free" label and take action against manufacturers that may be misleading consumers.

D. The conference committee and the Congress should pass a final version of CPSC reform legislation including the Feinstein amendment banning phthalates in children's products (incorporated as Section 40 of H.R. 4040 as passed by the Senate). The amendment will:

- Prohibit the use of phthalates (any combination of certain listed chemicals in concentrations exceeding 0.1 percent) in any children's product or child care article.
- Require manufacturers to use the least toxic alternative to phthalates.
- Prohibit the use of certain harmful alternatives—including substances known to be, likely to be, or suggestive of being carcinogens; and reproductive toxicants identified as causing either birth defects, reproductive harm, or developmental harm.
- The amendment also includes an important "savings clause" that would prevent Federal preemption of stronger state laws regulating phthalates in toys or other product categories.

Conclusion

We commend you, Mr. Chairman, for conducting this important hearing. We hope that you find our comments helpful. We look forward to working with you and your committee staff to move legislation addressing these concerns forward. We would also be happy to discuss other possible actions under the Committee's jurisdiction to protect consumers from the chronic and developmental hazards from unnecessary exposure to toxic chemicals like Bisphenol-A and phthalates in a variety of consumer products. Thank you.

Endnotes

[1] These reports and other information about toy safety are available at our website *www.toysafety.net.* Our main website is *www.uspirg.org*.

[2] Lead, of course, can also pose acute hazards, at the levels (up to 99 percent by weight) found in toy jewelry.

[3] The CPSC Reform Act was approved in Committee as S. 2045 (Pryor-Inouye) and a substitute was brought to the floor as S. 2663 (Pryor-Inouye-Stevens-Collins). The Senate bill's text was then substituted for that of the House bill and re-numbered on passage as H.R. 4040. The Feinstein phthalates amendment (Section 40) was accepted on voice vote on the floor.

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[18] Letter to the Honorable Deborah Platt Majoras, Chairman, FTC, November 21, 2005. On file with the author. Our petition was later denied.

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[24] vom Saal, F and C Hughes, An Extensive New Literature Concerning Low-Dose Effects of Bisphenol A Shows the Need for a New Risk Assessment. *Environmental Health Perspectives* 113:926–933 (2005). ("The charge to the HCRA panel, which was to perform a weight-of-the evidence evaluation of available data on the developmental and reproductive effects of exposure to BPA in laboratory animals, led to an analysis of only 19 of 47 available published studies on low-dose effects of BPA. The deliberations of the HCRA were in 2001–2002, and accordingly, a cut-off date of April 2002 was selected for consideration of the published literature. It is regrettable that the relevance of the analysis was further undermined by a delay of 2.5 years in publication of the report. During the intervening time, between April 2002 and the end of 2004, a large number of additional articles reporting low-dose effects of BPA in experimental animals have been published. The result is that by the end of 2004, a PubMed (National Library of Medicine, Bethesda, MD) search identified 115 published studies concerning effects of low doses of BPA in experimental animals.").

Senator KLOBUCHAR. Thank you, Ms. Hitchcock.

Senator Kerry has to leave and wants to say a few words before he goes.

Senator KERRY. I just wanted to thank the panel very much. I apologize that I cannot be here. I particularly want to thank Pete Myers, Dr. Myers, and Dianne Dumanoski and company for *Our Stolen Future,* just a superb piece of work which I wish more Americans were aware of. And Ms. Hitchcock, thank you for your testimony.

Now, I will submit some questions in writing, if that is permissible, and a fair number.

But I very much appreciate your testimony today. I apologize. We just have competing hearings, and I am sorry.

Senator KLOBUCHAR. Thank you.

Dr. Hentges?

STATEMENT OF STEVEN G. HENTGES, PH.D., EXECUTIVE DIRECTOR, POLYCARBONATE/BPA GLOBAL GROUP, AMERICAN CHEMISTRY COUNCIL

Dr. HENTGES. Thank you, Senator Klobuchar and Members of the Committee. The American Chemistry Council appreciates the opportunity to testify today and we also appreciate your interest in understanding the safety of plastics additives in consumer products.

We have also provided written testimony, and I ask that the written testimony be entered into the record.

We firmly believe that good public health policy must be based on facts and the best available science, and consumers should expect no less. Therefore, we are committed to the safety of our products, and last year alone, ACC member companies invested over $14 billion in environment, health, and safety programs helping to improve the understanding of our products.

As you know, much of the information on chemical safety can be highly technical and difficult for consumers to put into perspective. That is why it is essential for scientific review processes to be thorough and transparent in order for the public to have confidence in assessments conducted by Government experts.

Recent press reports have questioned the safety of phthalate esters and bisphenol A, compounds that are used in plastics to impart particular performance properties. Many of these reports have been misleading or inaccurate and have resulted in widespread confusion about the safety of plastics. In fact, both bisphenol A and phthalates have been subjected to numerous rigorous and comprehensive reviews by government agencies in the U.S. and around the world. After more than 5 decades of use, no reliable evidence has shown bisphenol A or phthalates in consumer products to have caused any harm to any person.

To the contrary, recent government reviews have affirmed the safety of bisphenol A and phthalates in common everyday products. The clear weight of scientific evidence provides reassurance that the public should not be concerned about everyday products that contain either bisphenol A or phthalates.

Phthalates are used to soften or plasticize otherwise rigid PVC plastic, which is used to make many consumer products. The U.S. Consumer Product Safety Commission, the National Toxicology program, and the U.S. Centers for Disease Control and Prevention have found no justification for restricting the use of phthalates as a plasticizer in toys and children's products. The CPSC conducted a 5-year health risk study and found no demonstrated health risk from the primary phthalate used in PVC toys or other products intended for children 5 years of age and younger and no justification for banning its use.

International scientific agencies have come to similar conclusions. The European Union conducted a decade-long risk assessment of five phthalates and concluded that the primary phthalate used in children's toys was unlikely to pose a risk to consumers following inhalation, skin contact, or ingestion.

In short, rigorous scientific reviews conducted by the government agencies responsible for regulating phthalates in consumer products do not support restrictions on the use of these materials. The science is simply not there to support such action.

Bisphenol A is used primarily to make clear, shatter-resistant polycarbonate plastic and durable epoxy resins, both used in a wide array of consumer products. In the past 2 years alone, 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 made from polycarbonate plastic and epoxy resins.

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 levels to BPA from food contact materials, including for infants and children, are below those that may cause health effects.

Based on the science, bisphenol A is not banned or restricted anywhere in the world. Although it has been claimed that low doses of bisphenol A may be harmful, the so-called low-dose hypothesis is just that, a hypothesis that has not been proven and has not been accepted by any of the government agencies that have reviewed the science on bisphenol A.

We understand that the public wants to be assured that the products they use are safe and have been evaluated using the best available science. We agree. In the case of phthalates and bisphenol A, 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 the opportunity to address the Committee.

[The prepared statement of Dr. Hentges follows:]

PREPARED STATEMENT OF STEVEN G. HENTGES, PH.D., EXECUTIVE DIRECTOR, POLYCARBONATE/BPA GLOBAL GROUP, AMERICAN CHEMISTRY COUNCIL

Summary of Testimony

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.

Bisphenol A

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 percent 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 • Headlamp lenses, mirror housings and bumpers • Instrument panels • Primer coatings • Fiber reinforced composites	*Building and Construction* • 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 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) that 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 con-

cerns. 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 early 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 Studies 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 U.S. 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 1 μg/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 3 μg/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 percent; 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 percent), at the top dose, on postnatal day 0 compared to controls. At study termination, a small but statistically significant decrease in body weight (4 percent) 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 percent) 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 percent) 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 percent) and in females (8–10 percent) 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 percent and 32–43 percent, 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 sta-

tistically significant increase in mean relative liver weight (9–26 percent) 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 percent resorptions per litter (40 percent as compared to 14 percent 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 percent, 1 percent, 9 percent and 14 percent 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 percent of fetuses malformed per litter or the percent 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 percent) and the gestation period (11–14 percent). 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 percent). Pregnancy rates were not affected by treatment with bisphenol A, nor was there any effect on the number of implantation sites per litter, percent resorptions per litter, number of live fetuses per litter, sex ratio, mean fetal body weight per litter, percent fetuses malformed per litter and percent 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 percent) 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 multigeneration 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 U.S. 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 U.S. 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 U.S.,[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 percent 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[59(k),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.[2] This value is identical to the Reference Dose set by the U.S. 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.

Phthalate Esters

The dozen or so phthalates in use today have thousands of applications. Their chief use is to make vinyl soft and flexible, without sacrificing its durability. They are used as softeners (or plasticizers) in toys, cars and products found in the home and in hospitals. For example, they are an important ingredient in life-saving and life-supporting vinyl medical devices. One member of the phthalate family is used in perfumes and other personal care products to make their fragrances last longer. Another type of phthalate is used in items such as tool handles and nail polish to help resist chipping.

Recent discussion regarding phthalates has focused on its use in toys and child care items. An extensive body of research on phthalates, including several recently completed U.S. and EU risk assessments, demonstrates that the use of phthalates, and in particular diisononyl phthalate (DINP), as a plasticizer in toys and objects used by children poses little to no risk to children.

With respect to toys and children's products, discussion typically focuses on the use of six phthalates: di(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), and butyl benzyl phthalate (BBP)—in the materials used in manufacturing toys or objects used by children, and another three—diisononyl phthalate (DINP), diisodecyl phthalate (DIDP) and di-n-octyl phthalate (DNOP)—in such products that children can put in their mouths.[62] This discussion apparently occurs because, despite the conclusions of the European risk assessments on phthalates, the EU acted to limit the uses of these phthalates in toys before the risk assessments were final.

In the late 1990s, a question arose as to whether use of phthalates in vinyl toys might present a health risk to children. The concern was based primarily on effects in rats that were treated with very high oral doses of phthalates, and on the knowledge that some phthalate could migrate out of vinyl toys if and when they were mouthed by children, and thus be ingested. At the time, information was sparse and uncertain regarding how much phthalate actually would migrate out of mouthed toys and the amount of time children actually mouthed toys. Initial calculations using very conservative assumptions for these parameters showed that exposure to phthalates would be lower than the levels at which effects are seen in animal studies, but that the margin of safety (MOS) might be less than considered desirable for DINP and DEHP.

In 1999, the EU instituted an emergency temporary ban on DBP, BBP, DNOP, DEHP, DINP and DIDP in toys intended to be put in the mouths of children under three, and began considering more permanent legislative measures.[63] At the same time, actions were initiated to bring more certainty to the science. The European Commission's Joint Research Center (JRC), the Netherlands' TNO Nutrition and Food Research Institute, the United States Consumer Product Safety Commission (CPSC), and the Canadian Ministry of Health (Health Canada) collaborated to develop a reliable method for measuring phthalate migration from mouthed vinyl toys. In the meantime, The EU was in the process of conducting in-depth and comprehensive risk assessments of DBP, BBP, DEHP, DINP and DIDP as part of its effort to evaluate and control risks from existing substances. In the U.S., the CPSC undertook an exhaustive assessment of the risks posed by DINP in children's toys, which included a state-of-the-art study of children's mouthing behaviors and migration testing using the method developed by the European/North American collaboration.

By 2003, these efforts had revealed that the risk posed by the use of DINP in children's toys—even those that are mouthed—is insignificant. The CPSC found that PVC toys and other items intended for children under five posed "*no demonstrated health risk.*"[64] The European Union's risk assessment for DINP concluded: *"The end products containing DINP (clothes, building materials, toys and baby equipment) and the sources of exposure (car and public transport interiors, food and food packaging) are unlikely to pose a risk for consumers (adults, infants and newborns) following inhalation, skin contact and ingestion."*[65]

Paradoxically, at the same time the science was providing reassurance about the use of phthalates in children's products, European politicians were urging more and more stringent restrictions on such use, resulting in the permanent ban in 2005 on the use DEHP, DBP and BBP in toys, and DINP, DIDP and DNOP in toys intended to be mouthed. Since 1999, the risk assessments conducted by the CPSC and the EU have provided high-quality scientific evidence that the use of most phthalate plasticizers, in particular DINP, in toys and children's articles poses little to no risk to children. Contrary to assertions made by some, there is little uncertainty about these conclusions. There are always remaining questions to be addressed by science; however, phthalates are among the best studied compounds in the world, and the risk assessments are based on recent, state-of-the-art studies.

In the meantime, early concerns from the 1990s about DEHP with respect to carcinogenicity observed in rodents following high dosing were investigated and addressed following additional research. In 2000, based on its judgment that the rodent results were not relevant to humans, the arm of the World Health Organization called the International Agency for Research on Cancer (IARC)—the international authority on cancer—changed its classification for DEHP to "not classifiable" as a human carcinogen. Regulatory agencies in Europe and Canada have also reached the same conclusion.

Accordingly, based on the science and the use patterns for phthalates, no restriction on the use of phthalates in toys and childcare articles is warranted at this time.

The United States Consumer Product Safety Commission Risk Assessment for Vinyl Toys Containing Phthalates Found Minimal to No Risk to Children Five Years of Age or Under

In late 1998, The National Environmental Trust and other organizations petitioned the U.S. Consumer Product Safety Commission (CPSC) to ban the use of polyvinyl chloride (PVC or vinyl) in products intended for children 5 years of age or under. A reason asserted for the ban was alleged health effects from the phthalate used as a plasticizer in vinyl children's products—diisononyl phthalate (DINP). The CPSC therefore undertook an intensive investigation of the toxicology of DINP and of potential exposure of children to DINP from vinyl products.[66]

For its review, CPSC convened a Chronic Hazard Advisory Panel (CHAP)—a seven-member panel of independent scientific experts who conducted a detailed review of the potential health hazards posed by DINP in products mouthed by children. The CHAP met three times over the course of a year and accepted voluminous comments from representatives of both industry and public interest groups. The 160-page CHAP report was published on June 15, 2001 and is available on the CPSC website.[67]

The CHAP found that 120 μg/kg/day was an Acceptable Daily Intake (ADI) of DINP for humans—*i.e.,* the amount of chemical a person can be exposed to on a daily basis over an extended period of time (up to a lifetime) with a negligible risk of suffering adverse effects. Based on this ADI, the CHAP concluded that a young child would have to routinely mouth DINP-plasticized toys for 75 minutes or more per day in order to pose a possible DINP exposure risk. However, finding no evidence that children mouth such toys for such extensive periods, the Report concluded that exposure to DINP for toys containing phthalates poses little or no risk of injury to children.

To verify these conclusions, the CPSC then conducted a state-of-the-art study of the amount of time children mouth objects, and it conducted additional studies of the rate of migration of DINP from vinyl when mouthed, using a methodology developed and validated by the TNO Nutrition and Food Research Institute, CPSC, Canada Health and the European Commission's JRC.[68] On September 23, 2002, the CPSC released a briefing package, summarizing the CPSC staff investigation of the potential risks of DINP in children's vinyl products.[69] The executive summary of that package states:

> Based upon the observation study, staff concludes it is very unlikely that children will mouth soft plastic toys for more than 75 minutes a day.[70]
>
> * * * * * * *
>
> The staff concurs with the CHAP conclusion that exposure to DINP from DINP-containing toys would be expected to pose a minimal to non-existent risk of injury for the majority of children. The new data from the behavioral observation study not only confirm this conclusion, but also demonstrate that children are exposed to DINP at lower levels than the CHAP assumed when it reached its conclusion. Also, since children mouth other products even less than they mouth toys and dermal exposure is expected to be negligible, there would be no jus-

tification for taking action against other products intended for children 5 years old and younger.

CPSC estimated that the most highly exposed group of children (those aged 3–12 months) had mean exposures to DINP of 0.07 μ/kg/day with a 95th percentile value of 0.44. This is well below the CHAP and CPSC conservative ADI of 120 μg/kg/day. CPSC also estimated worst case exposures hypothetically assuming that all toys, teethers and rattles were made with DINP-plasticized vinyl (in reality, only a portion of toys are made with soft plastic, only about a third of the soft plastic toys contain DINP, and no rattles or teethers contain DINP). Even under these conservative conditions, the estimated DINP exposures for children 3–12 months were 2.91 μg/kg/day (mean) and 10.71 μg/kg/day (95th percentile), still well below the ADI. Additional detail on the CPSC analysis is provided in Appendix 1.

The overall CPSC staff risk assessment information and conclusions have been published in the peer reviewed literature.[71] The authors conclude that *"oral exposure to DINP from mouthing soft plastic toys is not likely to present a health hazard to children."*[72]

On February 21, 2003, the CPSC Commissioners voted unanimously to deny the petition.[73] As indicated in the denial letter to petitioners, the Commissioners denied the petition based on the finding of CPSC that *"there is no demonstrated health risk posed by PVC toys or other products intended for children 5 years of age and younger."*[74]

The CPSC evaluation considered the conditions most likely to result in exposures of DINP to children and used very conservative (*i.e.,* health-protective) assumptions. CPSC considered children in those age groups that most often mouth items; it considered exposure from such mouthing, which would be expected to exceed that which could occur by dermal contact; and it conservatively evaluated situations in which DINP was assumed to be used to a much greater extent in children's products than it actually is. As explained in Appendix 1, the acceptable daily intake (ADI) used by CPSC also was quite conservative—a value 100 times below levels at which no effects have been observed in animal studies. Even with such conservatism, the potential exposures were still well below the ADI. Thus, the CPSC concluded no restrictions on the use of DINP in children's articles are warranted.

EU Risk Assessments Demonstrate That The Use of Phthalates in Vinyl Toys and Childcare Articles Poses Little or No Risk to Children

Like the CPSC assessment, the EU's risk assessments of phthalates support the safety of the use of phthalate esters in toys and children's products. As part of its existing chemicals program, the EU has published risk assessments for three of the six phthalates typically noted as of concern for children's products, DBP,[75] DIDP[76] and DINP,[77] and has completed draft assessments of BBP[78] and DEHP.[79] The remaining of the six phthalates, DNOP, has apparently not been the subject of an EU risk assessment because the production of this particular plasticizer ceased more than 10 years ago. The EU risk assessments, which incorporate the most modern and up-to-date data and methodology available to the EU, specifically include a consideration of risks to children from all potential sources, including toys and childcare articles.

The EU Risk Assessment for DINP Concurs With the CSPC Assessment, Finding No Likely Risk to Children

The most relevant EU risk assessment—that for DINP—was published in 2003. Unlike the CPSC risk assessment, which was intended only to determine the risk to children from mouthing objects, the EU assessment included an investigation of the risk to newborns, infants, children and adults from all routes of exposure. The EU assessment explicitly considered exposures of newborns, infants and children from multiple sources, including food and food-related uses, toys and baby equipment, car and public transport interiors, and building material and furniture. The EU risk assessment found no likely risk to humans under any exposure scenario. As stated in the risk assessment summary document with respect to consumer exposures:

> The end products containing DINP (clothes, building materials, toys and baby equipment) and the sources of exposure (car and public transport interiors, food and food packaging) are unlikely to pose a risk for consumers (adults, infants and newborns) following inhalation, skin contact and ingestion.[80]

The EU risk assessment also found no likely risk to adults, children or infants from environmental exposures, or from combined consumer and environmental exposures. The EU's finding of no risk to children under three was based on several calculated MOSs (Margins of Safety), all of which are above the CSTEE's recommended MOS

of at least 100. The EU risk assessment reported the following MOSs with respect to children:

- 176 (kidney effects) and 552 (fertility effects) for infants and newborns exposed to DINP from multiple consumer pathways, including toys;
- 107 (kidney and liver effects) and 336 (testicular effects) for infants for combined environmental and consumer exposures, including toys.

Thus, the most advanced and up-to-date EU risk assessment for DINP concurs with that of the CPSC: DINP exposure from the mouthing of soft plastic toys poses no likely risk to children. Further, the EU risk assessment for DINP demonstrates that exposure to DINP from other potential sources also poses no likely health risk. Under such circumstances, prohibiting the use of DINP in toys and childcare articles, whether or not they can be mouthed, is wholly scientifically unfounded.

U.S. National Toxicology Program Risk Assessments Support the Use of Phthalate Esters

The National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction (NTP) has completed extensive risk assessments on the six phthalates that are the subject of various legislative inquiries with respect to toys and children's articles. The NTP assessed risks to human reproduction and development by creating a 16-member independent panel of scientific experts that reviewed the toxicity and exposure information related to each phthalate. After three public meetings at which the key studies and issues were discussed, the expert panel issued a report to NTP for each phthalate. Based on the expert panel reports, NTP then published a Brief for each phthalate, in which it reported its level of concern that the various phthalates cause developmental or reproductive effects in humans. The NTP Brief, expert panel report and responses to public comments were combined in a Monograph published for each phthalate.[81] The NTP's conclusions for each phthalate were:

- For DINP, the NTP found *"minimal concern"* for developmental or reproductive effects in children;
- For DIDP, the NTP found *"minimal concern"* for developmental effects in fetuses and children;
- For BBP, the NTP found *"minimal concern"* for developmental effects in fetuses and children;
- For DBP, the NTP did not express a concern level for fetuses and children, primarily because of the low possibility of exposure from toys, but found *"minimal concern"* for developmental effects when pregnant women are exposed to average levels of DBP;
- For DNOP, the NTP did not express a concern level for fetuses and children, also based on the low possibility of exposure, but expressed *"negligible concern"* for effects on adult reproductive systems;
- For DEHP, the NTP expressed *"serious concern"* only for critically ill male prematurely born infants with very high medical exposures, *"concern"* for infants of mothers with intensive medical treatments, and *"some concern"* for children older than 1 year, based on very high assumed exposures from all sources.

In sum, the NTP risk assessments typically expressed minimal concern for adverse developmental effects in fetuses and children, in particular for DINP, the phthalate most commonly used in toys. The only concern above "minimal" expressed by NTP was for very high exposures to DEHP, which is not used in the manufacture of children's articles intended to be mouthed and therefore unlikely to approach these exposure levels.

An extensive body of research on phthalates, including several recently completed U.S. and EU risk assessments, demonstrates that the use of phthalates as a plasticizer in toys and objects used by children poses little to no risk to children.

Additivity is Not a Concern

Some have expressed concern that exposures to phthalates could be added up and that this total could present a health hazard. Currently, reports of human hazard associated with aggregate or cumulative exposures to phthalates are limited, and no reproducible evidence of human hazard has been reported. However, based on recent U.S. Centers for Disease Control (CDC) biomonitoring data, humans are exposed to extremely low levels of several phthalates simultaneously (the detection of multiple phthalate metabolites in the urine confirms exposure, but does not inform considerations of hazard or risk). Exposure data published by the CDC indicate that levels

of phthalates to which humans are exposed are much lower than doses with which additivity has been demonstrated in rodents.

It is also seen from the CDC data that maximum exposure in the most sensitive human subpopulations are still orders of magnitude less than doses with which additivity has been demonstrated in rodents.[82] Since the current reference dose for DBP (EPA IRIS) is 0.3 mg/kg/day, the estimated theoretical toxicity threshold for combined exposure to the most potent phthalate rodent toxicants DEHP, DBP, DIBP, and BBP would also be orders of magnitude higher than the RfD for DBP based on the simple dose addition model. It should be noted that synergistic effects—where the presence of one chemical enhances the effects of the second—do not appear to be seen in tests.

Recent Human Studies Contain Serious Flaws and Do Not Suggest a Need for Action

Several recent statistical studies have been cited as supporting the view that phthalates may pose risks of reproductive health risks to humans from phthalates. These studies, however, while suggesting areas where additional scientific inquiry is desirable, are by no means dispositive, and in some cases contradict earlier findings in rodent studies.

Main Study

Danish researcher Katharina Main and co-authors of the study, "Human Breast Milk Contamination with Phthalates and Alterations of Endogenous Reproductive Hormones in Infants Three Months of Age," have suggested that exposure to phthalates affect reproductive hormones in baby boys.[83] Main's study involved taking breast milk samples during the first three post-natal months from the mothers of 130 boys and analyzing the samples for various phthalate esters metabolites. Sixty-two of the boys exhibited cryptorchidism, and 68 did not. The study, however, does not support Main's claims because it found no association between phthalate monoester levels and cryptorchidism. In addition, there was no significant correlation between MEHP and serum samples of gonadotropins, sex-hormone binding globulin (SHBG), testosterone and inhibin B.

Hauser Study

A second frequently cited study, conducted by Hauser *et al.*, (2006), did not demonstrate an association between semen quality and levels of DEP metabolites in the urine.[84] The subjects were 463 males from subfertile couples and a group of control men. In general, the above statistical study provides results that are anecdotal in nature. They show a statistical association between a common chemical, or class of chemicals often used in personal care products, and a selected reproductive parameter. However, there is no causal relationship established, and there is no evaluation of other common, non-phthalate environmental chemicals. The latter evaluation would be necessary to establish that the increases in phthalate levels were not simply a biomarker of exposure to environmental chemicals in general, as opposed to a specific toxicant.

Swan Study

A third study which has been reported to associate phthalates with reproductive health risks was conducted by Shanna Swan *et al.*[85] This study was intended to test the hypothesis that *in utero* exposure to phthalic acid diesters blocks the action of testosterone in the male human fetus as reflected by changes in the anogenital distance (AGD), adjusted for body weight. Testosterone inhibition alters this parameter in reproductive tract studies of laboratory animals. This study examines statistical associations between physical genital measurements in 85 boys, up to 28 months of age, and a corresponding set of measurements of phthalate monoester metabolites in single spot urine samples collected from their mothers during the pregnancy. The hypothesis of Swan *et al. i.e.,* that exposures in the environment to several phthalates pose a hazard to male reproductive development, is not supported, however, due to five major flaws in the study:

1. The urine samples collected from the pregnant women are neither reliable nor valid for measuring their exposure to phthalates. The samples taken were not adjusted for variable fluid intake, were not adjusted for the time of day the samples were taken, and otherwise did not follow standard procedures, making the samples useless for obtaining accurate measurements of phthalate exposures.

2. The anogenital distance (AGD) measurement is of no known significance in humans. It is not a standard measurement in the practice of medicine and has never been related to any reproductive system problems. It is also difficult to measure accurately. Twenty percent of the boys measured were dropped from

the analysis because the researchers judged that reliable measurements could not be obtained for those boys. It is quite possible that many of the measurements on the remaining 80 percent also were not accurate.

3. Converting the AGD to an anogenital index (AGI) was an attempt to correct for varying weight and age, but ignores the fact that while the AGD does change with those two variables, the changes are not linear, and the correction is therefore incorrect. Also, the researchers did not compensate for other variables, like height or premature birth, in the infant's history.

4. In addition to the normal variations in weight and age, some measured infants were pre-term or even premature (which could well affect variables such as AGD, and genital effects), but were not excluded from the study.

5. It appears the researchers used the wrong statistical model to get their results. The statistical association claimed by the researchers is based on a model that predicts a relatively rapid decrease in AGI at low phthalate levels and much smaller decreases at higher levels. But this relationship is not biologically plausible; it should be the other way around. Thus, there is some question regarding the results of a study based on a possibly incorrect model.

The Swan study has been widely criticized as having significant flaws, and it is also noted as having been misreported by the press:

> [We] examined this study carefully and found some methodological problems, as well as a clear misinterpretation of the results by the press. The baby boys were not "demasculinized" in any way: the boys had a smaller anogenital index, which is a measure of the distance from the anus to the scrotum, adjusted for weight. In rats, under high doses of phthalates, this anatomical change also occurs, as does damage to the reproductive systems of the rats. In humans, no damage to the reproductive system was measured at all. And the shortened anogenital distance was well within normal ranges for baby boys. (See *http://www.stats.org/stories/WSJ__gives__skewed__phtha__oct05__05.htm*)

Colon Study

A Puerto Rican study measured blood levels of a variety of substances—including phthalates—in young Puerto Rican girls with a condition called thelarche, or premature breast development.[86] Reporting of the study results appeared to have caused confusion. In fact, the authors of the study stated that phthalate esters "cannot be interpreted as the cause of premature thelarche in Puerto Rican girls." Several key points in support of this conclusion follow:

1. Phthalates have been tested for their ability to act as estrogens. The weight of the scientific evidence demonstrates that these substances are not estrogenic.[2] Without a strong indication that phthalates could induce an estrogenic response in laboratory animals, it is unscientific speculation to suggest that estrogen-induced effects, such as thelarche, could be produced by phthalates.

2. The authors observe the possibility for multiple causes of thelarche: "It may well be that the etiology of the various manifestations of premature sexual development (including thelarche) on this island is multifactorial."

3. Thelarche has been studied for years. Researchers have identified numerous possible causes and the authors themselves note: "The following have already been associated with premature sexual development in Puerto Rico: the presence of anabolic steroids in poultry and consumption of soy-based formula with a high phytoestrogen content by Puerto Rican infants."

4. There is a considerable body of scientific research that indicates phthalates do not affect the female endocrine system. In a recent review of the data on phthalates, the National Toxicology Program Center for Evaluation of Risks to Human Reproduction (CERHR) Expert Panel expressed no concern related to developmental effects in girls from phthalate exposures.

The apparent high incidence of thelarche in this population seems unusual and warrants continued investigation. The Colon study does not show phthalates to be a causative factor and, for the reasons stated above, believes it is highly unlikely that phthalates are a factor for thelarche.

In general, the above statistical studies provide results that are anecdotal in nature. They show a statistical association between a common chemical, or class of chemicals used in personal care products, and a selected reproductive parameter. However, there is no causal relationship established, and there is no evaluation of other common, non-phthalate environmental chemicals. The latter evaluation would be necessary to establish that the increases in phthalate levels were not simply a biomarker of exposure to environmental chemicals in general, as opposed to a spe-

cific toxicant. Significantly, EPA has found that Swan and other epidemiological studies purporting to show a correlation between phthalate exposure and reproductive effects are unsuitable for use in the risk assessment process because they cannot demonstrate causation.[87]

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.

APPENDIX 1

Extended Summary of the United States Consumer Product Safety Commission Risk Assessment of the Phthlate Ester, DINP

In 1998, the United States Consumer Product Safety Commission (CPSC), in response to a petition from several organizations to ban the use of PVC in products intended for children 5 years of age or under, undertook a rigorous investigation of the toxicology of DINP and of potential exposure of children to DINP from vinyl products. As part of its investigation, CPSC convened a Chronic Hazard Advisory Panel (CHAP)—a seven-member panel of independent experts who conducted a detailed review of the potential health hazards posed by DINP in products mouthed by children. The CHAP report, which was published on June 15, 2001,[88] came to the following conclusions regarding overall risk from exposure to DINP:

- "The CHAP concludes that humans do not currently receive DINP doses from DINP-containing consumer products that are plausibly associated with a significant increase in cancer risk."
- "[T]he risk to reproductive and developmental processes in humans due to DINP exposure is extremely low or non-existent."
- "There may be a DINP risk to young children who routinely mouth DINP-plasticized toys for 75 minutes per day or more. For most children, exposure to DINP from DINP-containing toys would be expected to pose a minimal to non-existent risk of injury."

The CHAP based its conclusions regarding children's risk on a plausible upper-bound estimate of DINP exposure of 0.28 mg/kg/day for 0–18 month old children, assuming those children mouth soft plastic toys for 3 hours every day.[89] However, in reaching its conclusion, the CHAP emphasized the uncertainty associated with available DINP migration rate data, and questioned the robustness of existing mouthing behavior studies relied upon to calculate the upper-bound estimate, stating that "important covariates such as developmental age, physical condition, ethnicity, and other sociodemographic indicators are not reported."[90] Because of these uncertainties, the CHAP described its estimated child DINP exposures as "preliminary at best."[91]

To more accurately estimate potential child exposures to DINP, the CPSC conducted an extensive, state-of-the-art study to quantify the cumulative time per day that young children spend mouthing all objects, including toys, and conducted additional migration rate studies. The child mouthing study, described in Greene (2002)[92] and Kiss (2001),[93] was conducted in two phases, in which more than 550 children ranging in age from 0 through 36 months were observed and their mouthing behaviors recorded. In Phase 1, the mouthing behaviors of 491 children ages 0 through 81 months were observed and recorded to the nearest minute by their parents or legal guardians for four 15-minute periods over 2 days. In Phase 2, a trained observer observed and recorded the mouthing behaviors of 169 children (109 of whom had participated in Phase I) ages 3 through 26 months for a total of 4 hours on at least two different days. The observer conducted the observations at different times of the day, and if the child attended a child care facility outside the home, attempts were made to observe the child there as well. Children were selected to ensure that the subjects were reasonably representative of the overall population with regard to race, income, type of child care and gender.

The CPSC's mouthing study revealed that for all objects other than pacifiers, which do not contain DINP, estimated average daily mouthing times were:

- 70 minutes for children between 3 months and 1 year of age;
- 48 minutes for children between 1 year and 2 years; and
- 37 minutes for children between 2 and 3 years of age.

For all soft plastic items other than pacifiers, which comprise the items that could contain DINP, estimated average daily mouthing times were only;

- 1.3 minutes for the 3–12 month olds;
- 1.9 minutes for the 1–2 year olds; and
- 0.8 minutes for the 2–3 year olds.

Significantly, these data show that for even the youngest children, who typically mouth the most, the average mouthing time for all objects other than pacifiers is below the 75 minutes per day potential risk threshold identified by the CHAP. More importantly, the average amount of time children spend mouthing soft plastic toys, the objects that could contain DINP, is less than 2 minutes per day—far below CHAP's 75 minutes per day threshold, and far below prior mouthing estimates. In addition, these mouthing times are significantly lower than the times estimated by the Dutch Consensus Group study relied upon by the EU, which found average mouthing times for "plastic toys" of 17 minutes for 0–18 month olds.[94] As stated by the CPSC in its Executive Summary "[t]hese new mouthing data are much lower than earlier estimates and show an even smaller risk of exposure to DINP for children mouthing and chewing soft plastic toys."

In addition to the mouthing study, the CPSC also performed a migration rate study[95] using a modified head over heals (HoH) method developed and validated by the TNO Nutrition and Food Research Institute, CPSC, Canada Health and the European Commission's JRC.[96] CSPC tested 41 children's products that, according to their labeling, could be mouthed, sucked or chewed. Using the HoH method, the release of DINP was found to range from 1.05 to 11.09 μg/min/10cm^2.

Assuming that a child mouths a typical variety of objects and toys, the CPSC estimated that the most highly exposed group of children (those aged 3–12 months) had mean exposures to DINP of 0.07 μg/kg/day with a 95th percentile value of 0.44 μg/kg/day. These mean and 95th percentile exposure levels are, respectively, more than 1,700 and 270-fold below CHAP and CPSC's Acceptable Daily Intake (ADI) of 120 μg/kg/day.

The ADI is an estimate of the amount of chemical a person can be exposed to on a daily basis for an extended period of time (up to a lifetime) with a negligible risk of suffering deleterious effects. The ADI for DINP was calculated using a Benchmark Dose (BD_{05}) of 12 mg/kg/day and dividing by a 100-fold safety factor. The BD_{05} is generally considered more robust than a NOAEL, whose value is tied to an arbitrarily chosen dose level, because it takes into account all available dose response data. For DINP, the CPSC calculated the BD_{05} by fitting a mathematical model to pooled dose response data from two chronic exposure studies (Lington *et al.,* 1997;[97] Moore 1998[98]). In this case, the BD_{05} of 12 mg/kg/day is not only more robust than a NOAEL from a single study, but is more conservative, as its value is lower than either of the two studies' reported NOAELs. Thus, the CSPC data indicate that a typical child's exposure to DINP from soft plastic toys is well below the ADI, a conservative estimate of safe exposure levels of DINP.

In addition to estimating exposure to a typical child, the CPSC also conducted a worst-case exposure estimate, hypothetically assuming that all toys, teethers and rattles that the children mouthed were made with DINP-plasticized vinyl, when in reality, only a portion of toys are made with soft plastic, only about a third of soft plastic toys contain DINP, and no rattles or teethers contain DINP. Even applying these very conservative assumptions, the estimated DINP exposures for children 3–12 months were only 2.91 μg/kg/day (mean) and 10.71 μg/kg/day (95th percentile), still well below the CPSC's conservative ADI of 120 μg/kg/day.

On September 23, 2002, the CPSC released a briefing package that summarized the CPSC staff investigation of the potential risks of DINP in children's vinyl products.[99] The executive summary of that package states:

> Based upon the observation study, staff concludes it is very unlikely that children will mouth soft plastic toys for more than 75 minutes a day.[100]
>
> * * * * * * *
>
> The staff concurs with the CHAP conclusion that exposure to DINP from DINP-containing toys would be expected to pose a minimal to non-existent risk of injury for the majority of children. The new data from the behavioral observation study not only confirm this conclusion, but also demonstrate that children are exposed to DINP at lower levels than the CHAP assumed when it reached its conclusion. Also, since children mouth other products even less than they mouth toys and dermal exposure is expected to be negligible, there would be no justification for taking action against other products intended for children 5 years old and younger.

The overall CPSC staff risk assessment information and conclusions have been published in the peer reviewed literature.[101] In this publication, the authors state that they "conclude that oral exposure to DINP from mouthing soft plastic toys is not likely to present a health hazard to children."[102]

On February 21, 2003, the CPSC Commissioners voted unanimously to deny the petition to ban the use of PVC in products intended for children 5 years of age or under.[103] As indicated in the denial letter to petitioners, the Commissioners denied the petition based on the finding of CPSC that "there is no demonstrated health risk posed by PVC toys or other products intended for children 5 years of age and younger."[104]

Endnotes

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[2] European Commission. April 17, 2002. Opinion of the Scientific Committee on Food on Bisphenol A. Available at *http://ec.europa.eu/food/fs/sc/scf/out128_en.pdf*.

[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.

[4] European Union Risk Assessment Report—4,4'-isopropylidenediphenol (Bisphenol-A). 2003. Available at *http://ecb.jrc.it/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/SUMMARY/bisphenolasum325.pdf* (summary) and *http://ecb.jrc.it/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/REPORT/bisphenolareport325.pdf* (full report).

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[63] *See* ENDS Environment Daily, EU phthalate ban decision postponed, November 22, 1999, available at: *www.environmentdaily.com/articles/index.cfm?action=article&ref=6501.* At that time, members of CSTEE questioned whether the science supported a finding of an immediate risk and expressed their disagreement with the imposition of the emergency ban.

[64] CPSC, Petition Denial at 3 (quoting Memorandum from Marilyn L. Wind to the Commission, Response to Petition HP 99–1 (August 13, 2002), at 16–17).

[65] European Chemicals Bureau (2003). 1,2-Benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich and di-"isononyl" phthalate (DINP), CAS Nos: 68515–48–0 and 28553–12–0, EINECS Nos: 271–090–9 and 249–079–5, Summary Risk Assessment Report, Special Publication I.03.101, p. 18, available at *http://ecb.jrc.it/*.

[66] A more extensive summary of the CPSC report is attached to these comments.

[67] CHAP (2001). Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Diisononyl Phthalate (DINP), June 2001, available at *http://www.cpsc.gov/LIBRARY/FOIA/Foia01/os/dinp.pdf.*

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[70] CPSC's mouthing study found that children's mouthing times for soft plastic objects was less than 2 minutes per day. *Id.*

[71] Babich, M., Chen, S-B., Greene, M., Kiss, C., Porter, W., Smith, T., Wind, M. and Zamula, W. (2004). Risk assessment of oral exposure to diisononyl phthalate from children's products. *Regulatory Toxicology and Pharmacology* 40:151–167.

[72] *Id.* at 165.

[73] Letter from Todd A. Stevenson, Secretary, CPSC, to Jeffrey Becker Wise, Policy Director, National Environmental Trust (February 26, 2003) (Petition Denial); available at *http://www.cpsc.gov/library/foia/foia03/petition/Ageunder.pdf.*

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[75] European Chemicals Bureau, European Union Risk Assessment Report: Dibutyl Phthalate, CAS No: 84–74–2, EINECS No: 201–557–4, Risk Assessment, with Addendum to the Environmental Section—2004, 1st Priority List, Volume 29 (2003).

[76] European Chemicals Bureau, European Union Risk Assessment Report: European Chemicals Bureau, European Union Risk Assessment Report: 1,2-Benzenedicarboxylic Acid, Di-C9-11-Branched Alkyl Esters, C10-Rich and Di-"Isodecyl" Phthalate (DIDP), CAS Nos: 68515–49–1 and 26761–40–0, EINECS Nos: 271–091–4 and 247–977–1, Risk Assessment, 2nd Priority List, Volume 36 (2003).

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[81] The NTP Monographs are available at: *http://cerhr.niehs.nih.gov/reports/index.html*.

[82] Maximum estimated human daily exposure to one of the most commonly used phthalates, DEHP, was calculated from measurements in children aged 3–14 (3.1 µg/kg/d).

[83] K.M. Main *et al.,* "Human Breast Milk Contamination with Phthalates and Alterations of Endogenous Reproductive Hormones in Infants Three Months of Age," *Environmental Health Perspectives* 114 (2006).

[84] R. Hauser *et al.,* Altered Semen Quality in Relation to Urinary Concentrations of Phthalate Monoester and Oxidative Metabolites," *Epidemiology 17,* no 6 (2006).

[85] S. H. Swan *et al.,* "Decrease in Anogenital Distance among Male Infants with Prenatal Phthalate Exposure," *Environmental Health Perspectives* 113 (2007).

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[87] See, EPA Draft Toxicological Review of Dibutyl Phthalate (Di-n-Butyl Phthalate): In Support of the Summary Information in the Integrated Risk Information System (IRIS), available at: *http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=457421*.

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[92] Greene, M.A. (2002) Mouthing times among young children from observational data. U.S. Consumer Product Safety Commission, Bethesda, MD.

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[100] CPSC's mouthing study found that children's mouthing times for soft plastic objects was less than 2 minutes per day. *Id.*

[101] Babich, M., Chen, S-B., Greene, M., Kiss, C., Porter, W., Smith, T., Wind M. and Zamula W. (2004). Risk assessment of oral exposure to diisononyl phthalate from children's products. *Regulatory Toxicology and Pharmacology* 40: 151–167.

[102] *Id.* at 165.

[103] Letter from Todd A. Stevenson, Secretary, CPSC, to Jeffrey Becker Wise, Policy Director, National Environmental Trust (February 26, 2003) (Petition Denial); available at *http://www.cpsc.gov/library/foia/foia03/petition/Ageunder.pdf*.

[104] Petition Denial at 3 (quoting Memorandum from Marilyn L. Wind to the Commission, Response to Petition HP 99–1 (August 13, 2002), at 16–17).

Senator KLOBUCHAR. Well, thank you very much, Dr. Hentges, and to all the witnesses.

Dr. Myers, your research seems to point to the fact that we have a long way to go before finding out the full effect of certain phthalates in PVC plastic or BPA in our food and beverage containers. Are there any studies that you know of that are looking into the low dosage exposure to which you referred in your opening statement?

Dr. MYERS. Yes, there are studies underway, both experimental with animals and epidemiological studies of people. There is a center at the University of Rochester that is leading the way in both looking at the effects of exposure to individual phthalates as well as mixtures of phthalates and bisphenol A. It is a very interesting, cutting-edge area of science right now.

Additionally, there are efforts underway in California with Stanford University and the University of Missouri also looking at a prediction that arises out of some very interesting science on bisphenol A, that there should be an association between low levels of bisphenol A and an increase in the rate of spontaneous mis-

carriage in people. That study is now funded and we are anxiously awaiting for the results.

Senator KLOBUCHAR. You mentioned that study. Was that the Center for Disease Control that showed this high amount of additives in individuals tested?

Dr. MYERS. No. The studies that I just referred to——

Senator KLOBUCHAR. It was in your opening. No, no, no. In your opening statement when you talk about the high amount of——

Dr. MYERS. Oh, when I said that the levels in people today are above those——

Senator KLOBUCHAR. Higher than animals.

Dr. MYERS.—sufficient to cause harm in animals, that is the result of an analysis done by 38 leading scientists on bisphenol A that were brought together with funding from the National Institutes of Health a year ago November. And as part of an extensive review of the BPA literature, the scientists there, led by a professor from the University of Missouri named Wade Welshons, took the existing data and did some new analyses asking how can we compare what is in animals when we see adverse effects. What is in the serum of those animals and how does that compare with data from the serum of people, the average level in Americans today? And what that analysis concluded—and it is published now in *Reproductive Toxicology*. It was published in August of 2007. What that study concluded was that the average levels in people are above those sufficient to cause harm in animals.

And another interesting thing about that analysis was that it reveals that if you look at what is in people today, we cannot explain it based on known sources of exposure. Actually one of the things the Consumer Product Safety Commission ought to be looking at is the use of BPA in thermal paper. It is widely used in thermal paper. Those receipts you get when you go to the gas station, whatever. At least in some formulations of that thermal paper, the concentrations of bisphenol A dust are quite high.

Senator KLOBUCHAR. Can you talk about the life cycle of those additives in your system?

Dr. MYERS. They are metabolized.

Senator KLOBUCHAR. Do they go away?

Dr. MYERS. They go away relatively rapidly, and that is one of the challenges. If they go away as rapidly as they do, which they do, why is that we find the levels that we find in people? There are some significant sources of exposure that we have not yet identified. It is not just coming in from food.

Senator KLOBUCHAR. One of the groups came in to talk to us about this. They talked about how a ban on the phthalates or the BPA would lead manufacturers to use plastic additives that have not even been tested yet. What are the alternatives?

Dr. MYERS. There certainly are alternatives for some uses. I was in Japan last November in the Christmas shopping season, and bisphenol A is not allowed to be used. Manufacturers in Japan have chosen not to use polycarbonate plastic for kids' toys and they do not allow the phthalates in kids' toys. And there is no lack of toys in Japanese stores during Christmas shopping time.

We have heard that Nalgene has committed to replacing bisphenol A in its bottles. They are using a couple different formu-

lations, one they have used for a long time, polypropylene, which is, as far as we can tell, perfectly safe. They have now introduced two new types, one of which is stainless steel which looks to be fine. It is not a plastic. We are not sure about the other one, and some testing should be done on that.

Senator KLOBUCHAR. Dr. Hentges, did you want to comment on that?

Dr. HENTGES. Any specific part of it you would like?

Senator KLOBUCHAR. Well, I was asking him about what these products would be replaced with if we make a decision, as many manufacturers are starting to do, to make phthalate-free products.

Dr. HENTGES. Right. Well, if we think about why products are used, they are used because of the attributes, the properties they have. So, for example, polycarbonate plastic is used because it is clear. It is highly shatter-resistant, and it has other useful properties as well. Epoxy resins, also made from bisphenol A, are used because they also have a fairly unique set of properties.

So to replace those, there are a couple of initial hurdles that have to be gone over. One is to find something that performs because these products perform a function. They are used for something. So we have to find an alternative that works at least as well as what we are replacing.

But then since we are talking here about safety, we also have to be sure that these products really are at least as safe as what we are replacing. And in the case of bisphenol A, there are no alternatives that have been tested as thoroughly as bisphenol A, that have been vetted so carefully, so frequently by government agencies around the world.

So we have two very big challenges in order to find alternatives that we can be confident are going to be better than what we have today.

Senator KLOBUCHAR. But I showed those two bottles over there, the Nalgene bottles, and they did one that did not have the BPA in it. Are you saying that is not safe then?

Dr. HENTGES. No. I am not saying it is not safe, but it is made from something. I do not know what it is made from. I cannot tell by looking at.

Senator KLOBUCHAR. I can give it to you.

Dr. HENTGES. Well, I still probably could not tell by looking at it, but it is made from something. And the question then is, how much data is available to know that that something is safe?

Again, the benchmark that I can speak to is bisphenol A because we have an extraordinarily rich scientific database there that supports the safety of bisphenol A, and that data has been reviewed repeatedly around the world, leading to the conclusions that you have heard, that bisphenol A is safe for use in that kind of a product.

Senator KLOBUCHAR. Now, your testimony does admit to evidence that an infant can be harmed by phthalates if she mouths a plastic toy for about an hour. Would that be a correct characterization?

Dr. HENTGES. I think on that question, I am going to have to beg off. I do not have the great personal knowledge on phthalates, but I can commit to providing a written answer on that one as a follow up for the record.

Senator KLOBUCHAR. OK. Well, we are going to find it in your testimony here, if we could just take a second.

Dr. HENTGES. It is the follow up questions where I am going to have some difficulty because——

Senator KLOBUCHAR. OK, but you do remember saying that?

Dr. HENTGES. I can read what I said.

Senator KLOBUCHAR. It is in the written testimony.

Dr. HENTGES. Oh, the written, OK.

Senator KLOBUCHAR. I think here you say based on this ADI, it was concluded that a young child would have to routinely mouth the plasticized toys for 75 minutes or more per day in order to pose a possible DINP exposure risk.

Dr. HENTGES. I will commit to coming back with a written response for the record on that.

Senator KLOBUCHAR. OK.

We have also heard testimony that when boiling water is poured into a bottle that contains BPA, it could create a problem.

Dr. HENTGES. That I can speak to. There are quite a few studies that examine polycarbonate baby bottles. Usually it is baby bottles that are tested to understand how much bisphenol A can leach out of those under a very wide range of conditions. And some of the best data has been published very recently. Several studies have been published by different institutions in Europe, and one of those studies specifically looked at—all of them together look at a wide range of real-life use conditions. But one of them looked, in particular, at the effect of temperature and, in particular, the effect of pouring boiling water directly into the bottle. And what these studies collectively found is that there are really no real-life use conditions that would lead to an unsafe situation where the level of bisphenol A could be harmful, that it could exceed a safe level. And in particular, even when boiling water was poured into the baby bottles, that did not lead to an unsafe condition.

Senator KLOBUCHAR. But is that not, as Dr. Myers was saying, based on these high levels of the chemical as opposed to some of the low-dose levels that he is talking about?

Dr. HENTGES. No.

Senator KLOBUCHAR. Then why would this company change their product in response to concerns about this?

Dr. HENTGES. Well, let me start with the first part. In Europe, where these studies on baby bottles were conducted, just about 1 year ago, the European Food Safety Authority published their report on the safety of bisphenol A. And this was a comprehensive evaluation of the available science, and it included—in fact, it was probably largely focused on studies that examined low doses, low levels of bisphenol A. Based on all of those studies, based on the weight of evidence from those studies, they established what they call a Tolerable Daily Intake or, in simple terms, a safe level.

Then comparing that to the levels that came out of the baby bottles in those studies that I referred to, those levels are far lower than the safe level that was determined based on studies that looked at low doses of bisphenol A.

Senator KLOBUCHAR. Dr. Myers, do you want to respond?

Dr. MYERS. Yes. It is simply not true. The levels of bisphenol A that will leach out of baby bottles—and studies in the United

States have shown this—are within the range that cause harm in animals at low doses. That is a matter of—it is in the scientific literature.

Senator KLOBUCHAR. Ms. Hitchcock, do you want to respond at all?

Ms. HITCHCOCK. No.

Senator KLOBUCHAR. OK. Thank you very much. I appreciate it.

Senator PRYOR [presiding]. Thank you, Senator Klobuchar. Thank you for covering for me. I had to do a quick conference call in the back room, and I apologize for my absence.

Let me follow up on that, if I can. There are clearly two strong opinions on the safety level, and I think one of the reasons there might be two strong opinions is—is it possible that you all are looking at different studies, or are you just interpreting the same studies differently? Do you want to take a stab at that?

Dr. MYERS. Sure. The studies that I am looking at typically are funded by the National Institutes of Health. It is very interesting. The studies by the National Institutes of Health typically do not begin with a toxicological perspective. They look at different endpoints, and they use much more sophisticated tools to get at what are the biological mechanisms underlying impacts that they are seeing. These are studies that are published in the proceedings of the National Academy of Sciences. They are published in *Science* and *Nature,* in the premier scientific journals of the world. And the bulk of those, over 90 percent of those studies, show adverse effects in animals at low levels.

Those are the studies that I think we need to be looking at because they are asking—in my opening my comments, I talked about a new way—a new framework for thinking about toxicology and how the EPA and the FDA and the Consumer Product Safety Commission are really missing the boat on this because they are focused on old toxicological endpoints. They are not using modern molecular genetics in their work. So I am looking at new science. They are looking at old science.

Senator PRYOR. Do you have a comment on that?

Dr. HENTGES. Yes. Going back to where you started, are we looking at different studies, no, I do not think we are looking at different studies. We all have the same body of scientific information to look at, and there are, indeed, many hundreds of studies on bisphenol A. But those studies vary vastly in size, scope, quality, relevance to human health. There is no single study that is really going to give us the answer about whether bisphenol A is safe or not.

We review all of those studies together in a weight of evidence fashion, and our conclusion is that bisphenol A is safe for use in consumer products of the type that you are considering. But more important than our view is the view of the many independent scientific and government bodies around the world who have also reviewed the science, who have reviewed all of it together and drawn a conclusion based on the full weight of scientific evidence. Those conclusions, more importantly, support the safety of consumer products made from bisphenol A.

Senator PRYOR. Let me, if I can, ask each of the three of you the same question. I will go ahead and start with you, if I may. That

is, are you satisfied with the job the FDA and the CPSC have done on these chemicals that we have been talking about today?

Dr. HENTGES. Well, focusing on FDA and bisphenol A, because they regulate food contact products made from polycarbonate plastic or epoxy resins, we do have confidence that FDA has been monitoring the science quite carefully. We believe that they have the scientific capability and credibility to do that. We have, however, because there is new information available from the recent reports, encouraged FDA to refresh their view, to update, make sure they have looked at everything, and provide their conclusions. That is very important because consumers are getting a lot of confusing and conflicting information, and we believe that FDA has the capability to cut through that confusion and provide a clearer view to consumers about the safety of products made from bisphenol A.

Senator PRYOR. By the way, consumers and the U.S. Senate are getting confusing information. There is a sharp disagreement here.

But Ms. Hitchcock, would you like to answer whether you think FDA and CPSC are doing a good job to date?

Ms. HITCHCOCK. In the presence of the confusing information that consumers and the U.S. Senate are getting about bisphenol A and about phthalates, I would say no. And we would urge them to do a better job. I noted in my testimony that we need to reform U.S. chemicals policy so that we are not testing chemicals that are on the market on our children and on ourselves before we actually know what the effects are. We are hearing from two scientists here and we are hearing a diversity of opinion about the safety of these chemicals. Where there is a doubt, we ought not be putting them in the hands and the mouths of our children.

Senator PRYOR. Did you have a comment?

Dr. MYERS. My comment will not surprise you, Senator. I think the FDA right now is failing the American people miserably. We have seen that in other cases over the last year. It is no different here. They are not asking the right questions. They are not using modern scientific methods to ask those questions. Molecular genetics, as it has developed over the last 15 years, has changed the types of questions we should be asking about how contaminants can interfere with health. We used to worry about high doses causing mutations, high doses causing birth defects directly. Now we know that low doses, by interfering with how genes are being turned on and off during development, can have profoundly important health consequences that are not revealed by the procedures that the FDA, the EPA, and the CPSC use today.

We have been blind-sided by these effects. These things are well known to endocrinologists, medical practitioners of the science of endocrinology. It is not something new to them. It is only when over the last 15 years we have learned that some contaminants possess characteristics like hormones that we have realized we have not been asking the right questions. And that is actually a much bigger challenge than just dealing with BPA and phthalates. There are probably a lot of other contaminants that share these characteristics. In fact, we know there are, and we are similarly being blind-sided on those cases as well.

Senator PRYOR. I really did not have any more questions. I know that some of our colleagues will have questions that they will sub-

mit in writing, and we would like to leave the record open for 2 weeks and allow Senators to ask questions and would love a timely response when you all receive those.

But I do want to thank you. This is an important issue. I really think the sharp disagreement on this panel underscores the reason we had this hearing in the first place—to try to start the process for the Senate and the Congress to really get to the facts of this. It may be what you said a few moments ago. It may be that the Government needs to update and upgrade their testing capabilities, and that may solve this problem. Then again, it may be that these chemicals are safe, if we did that.

But I do think it is important for us, the American Government, to get our policy right. And I do think, Ms. Hitchcock said something that most Senators would agree with. If there is a substantial risk, even if it is not exactly known exactly what the level is, err on the side of caution, especially when it comes to children. I think you are going to see that here in the Senate.

So I would appreciate you all continuing to work with us and continuing to talk to us and our staffs about where you think this should be heading. We know Senator Schumer has a bill. We know that there are others out there who are working on legislation in different forms and fashion. So this is going to be an issue that we will continue to work through.

So, again, I want to thank this panel and the previous panels for being here.

This hearing is adjourned.

[Whereupon, at 12:06 p.m., the hearing was adjourned.]

A P P E N D I X

RESPONSE TO WRITTEN QUESTIONS SUBMITTED BY HON. DANIEL K. INOUYE TO NORRIS E. ALDERSON, PH.D.

Question 1. What research is being done to determine the effects these chemicals have on wildlife?

Answer. FDA's primary concern in evaluating the safety of these chemicals under the Federal Food, Drug, and Cosmetic Act is their potential for human health effects. Numerous studies in the literature have been conducted to evaluate the effects of these chemicals on assessments of both human and ecological health. Accordingly, some of the studies that FDA relies on in making human safety decisions could potentially be applied to the safety of wildlife. The Environmental Protection Agency (EPA) or the Department of the Interior (DOI), however, would be the appropriate Federal entities to address the effects on wildlife.

Question 2. What are the known effects of these harmful plastic chemicals on wildlife?

Answer. There are many issues with regard to the disposal of plastics and its potential harm to the environment, including wildlife. Again, although FDA considers all relevant safety data when reviewing uses of food additives for human consumption, either EPA or DOI is better suited to address these issues.

Question 3. Is there any evidence that humans can be exposed to these chemicals through the food, specifically seafood, which we eat?

Answer. Yes, consumers may be exposed to BPA and phthalates as a result of their authorized uses in food contact materials. We are limiting our comments to that exposure source.

Bisphenol-A (BPA) is a chemical building block of epoxy-based enamels used in food cans. These epoxy enamels are used to coat the inside of food cans to impart resistance to corrosion of the metal by the packaged food. By controlling degradation of the can, food is preserved from microbiological contamination. Many foods, including seafood products, are packaged in cans coated with epoxy enamels. Consumers may be exposed to minute amounts of BPA as it may migrate from the epoxy coating to food during storage.

Phthalate plasticizers are approved for use with some food wrapping polymers where they impart cling and flexibility properties to the wrap. Although phthalate plasticizers have been authorized for such uses for many years, FDA's research of the regulated industry indicates that these uses have been largely discontinued, and nearly all currently available commercial food wraps are either unplasticized polyolefin materials having no phthalates, or are materials plasticized with alternate materials (such as citrates). It might be possible to find some polyvinyl chloride or polyvinylidene chloride food wraps on the market that are still plasticized with phthalates, and if those wraps were used; some phthalate plasticizer would be transferred to the food. The higher the fat content of the wrapped food, the more phthalate plasticizer would be transferred. Accordingly, the amount of phthalates in the food would vary based on the wrap used to prepare seafood for sale and the amount of fat content in the seafood. For this reason some phthalates such as Di-2-ethylhexyl phthalate are restricted from use in contact with high fat content foods.

RESPONSE TO WRITTEN QUESTIONS SUBMITTED BY HON. MARK PRYOR TO NORRIS E. ALDERSON, PH.D.

Question 1. The U.S. National Toxicology Program released a report, in early April, regarding the reproductive and developmental hazards associated with bisphenol-A (BPA). Shortly after the report was released the FDA announced that it would look into the safety of baby bottles, formula cans, and other products made with BPA. What has the FDA done to move this investigation forward?

Answer. Commissioner of Food and Drugs Andrew C. von Eschenbach, M.D. has formed an Agency-wide BPA Task Force 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, and is actively reviewing the National Toxicology Program's (NTP) Draft Brief. Members of the Task Force have met with NTP staff to discuss their findings and better understand NTP's approach to evaluating the underlying data. Also, staff of FDA's National Center for Toxicological Research (NCTR) is discussing with NTP additional research needs relating to 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 and is reviewing other potential routes of exposure. Additionally, the Task Force has been talking with representatives of product manufacturers to better understand manufacturing and chemistry issues. Finally, the Task Force is considering what recommendations for further laboratory studies or other research may be appropriate.

Question 2. How long do you anticipate for a final conclusion or ruling from the FDA regarding possible health risks caused by BPA exposure?

Answer. In late summer or early fall, the BPA Task Force is expected to issue its draft report. At FDA's request, the FDA Science Board, which is an independent advisory body to FDA on scientific issues, is forming a subcommittee on BPA to undertake scientific peer review of the Task Force report. Part of that peer review process will be to hold a public meeting to accept input and comments from the public. The full Science Board will receive the findings of the subcommittee during its fall meeting.

Question 3. The "low-dose hypothesis" claims that exposure to extremely low levels of certain substances could cause adverse health effects in humans. Some have criticized existing studies and reviews for looking at only high dosage exposure. Have any of the governmental reviews done by FDA taken into account studies showing adverse health effects from low-dose exposure to BPA?

Answer. FDA's formal re-evaluation of BPA conducted over the past 14 months has considered many studies designed to investigate so-called "low" dose effects. Two of these studies, which were designed based on international regulatory study guidelines, and included a wide range of doses, including low doses, and expanded protocols, did not demonstrate adverse health effects in rodents from low dose administration of BPA. The two pivotal studies were published by Tyl *et al.,* in 2002 (rat study) and 2008 (mouse study).

Our current review effort is ongoing regarding the concerns which the most recently completed assessments (NTP's Center for the Evaluation of Risks to Human Reproduction (CERHR) Expert Panel Report, the NTP Draft Brief and the Health Canada Draft Screening Assessment) have highlighted. The BPA Task Force review is considering numerous additional "low" dose studies and will address the more recent concerns raised for low-dose effects.

Question 4. The results of studies into the potential health effects of BPA and phthalates conducted by the government, industry, and some in academia seem to vary quite widely in their results. How would you explain these differences?

Answer. There are various factors that may account for differences in study outcomes independent of the source of information, the performers of the study, or the sponsors of the study. Studies conducted in laboratories in academia are more hypothesis-driven as opposed to safety evaluation studies and as such, FDA has encountered limitations in the methodologies, reporting, or relevance of the endpoints of analysis with regard to their utility in safety assessments. FDA has published guidance on the conduct of studies for submission to the Agency to support the safe use of food additives (*Toxicological Principles for the Safety Assessment of Food Ingredients: Redbook 2000*). This guidance is intended to help ensure the use in safety assessments of studies that are conducted using good laboratory practices (GLP) and quality assurance (QA), sufficient and relevant dosing protocols, adequate replicates of animals for meaningful statistical analysis, interim analysis when applicable, and analysis of endpoints (organ weights, clinical chemistry, histopathology, etc.) which have been validated by FDA or other international regulatory organizations. In addition to FDA, other international agencies involved in regulatory toxicology also provide guidance that is useful for conducting safety assessments.

A typical GLP study submitted to FDA contains all the raw data collected during the course of the study, thereby allowing the Agency to review and audit the study and reach an independent conclusion on the findings reported by the study author(s). As journal publications typically are limited in the thoroughness in which

they are reported, FDA is ordinarily unable to validate the performance quality or data integrity of these studies. By contrast, FDA's standard review procedures for reported GLP/QA studies allow FDA to independently reach the authors' conclusions or arrive at alternative interpretations of the data and findings presented. In addition to reporting limitations, many of the studies in the literature fail to control for numerous issues that validated regulatory protocols eliminate by design. These shortcomings cannot be ignored in an overall weight of evidence analysis of a food additive's safe use.

Question 5. Does the FDA take into account the safety of these chemicals when rendering its opinions?

Answer. Yes, FDA is required by statute to judge the information relevant to the safety of chemicals used in food contact material according to the safety standard for food additives. That standard is a "reasonable certainty of no harm" (see Title 21, *Code of Federal Regulations* § 170.3(i)). To accomplish this, FDA requires that industry sponsors provide all relevant safety data (including data indicating potential harm) and to produce any additional data necessary to establish the safety of the intended use.

Question 6. Please explain the significance of low-dose exposures to BPA and how it relates to the traditionally held belief of "the dose makes the poison"?

Answer. The expression "the dose makes the poison" refers to the fact that all substances can produce toxicity given a high enough dose. A common extreme example is hypnoatremia—a toxic effect observed in individuals who consume dangerously large quantities of water resulting in a reduction of essential minerals in the blood. For chemicals that enter the food supply, FDA typically estimates a safe or acceptable level by determining the no observed adverse effect level in animal testing and extrapolating to a safe level of human consumption that is ordinarily 100 to 2,000 times (or more) smaller. In this regard, FDA's approach is based on the entire body of toxicological safety testing research; that research generally supports the fact that increasing exposure to a chemical increases the toxic effect and that potential toxicity can be mitigated by limiting exposure to levels many times lower than those that show only limited toxicity in experiments.

Exposure to residual BPA through uses in food additives is relatively low, at ≤ 11 micrograms per person per day (μg/person/day). Traditionally, FDA's evaluation of chemical migrants to food from the use of food contact materials at exposures of ≤ 150 μg/person/day focuses primarily on carcinogenicity and genetic toxicity as an indicator of carcinogenicity, unless data are available (biological or predictive) that indicate a concern for another endpoint of toxicity at this level. However, BPA has been studied for many years with regard to its potential ability to bind to estrogen receptors and either mimic estrogen or disrupt normal endocrine activity. Since estrogens and other hormonally active compounds with high affinities to steroid receptors can show effects at low doses, research has focused on BPA's ability to disrupt normal hormonal activity or act as a reproductive or developmental toxicant. However, BPA is only weakly estrogenic (several orders of magnitude less than estrogen) and BPA is metabolized extremely quickly into BPA-glucuronide (BPAG), which is estrogenically inactive. Although FDA's review of the most recently raised concerns for BPA is not complete, previous reviews have determined the margin between no effect levels in animal tests and human exposures to be acceptable based on FDA's routinely used margins of safety.

Question 7. How is the average person exposed to phthalates? What is the best way to reduce exposure to phthalates?

Answer. In terms of food contact applications, 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) is tracking the reductions in use of phthalates in food contact materials as well as the development of new toxicological data. CFSAN has established a Phthalate Task Group (PTG), whose primary focus will be to determine the most realistic exposure estimation and better characterize any potential risk associated with phthalate use in food packaging.

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 professionals 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 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. 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.

Question 8. Please explain the significance of phthalate mixtures.

Answer. Regarding the toxicological significance of phthalate mixtures, there have been reports in the literature that individual phthalates with a similar mode of action can induce dose-additive effects when administered as a mixture.

Question 9. What are endocrine disruptors and how do they affect us?

Answer. Endocrine disruptors are exogenous substances (natural or synthetic) that act like hormones and, by doing so, have the potential to either mimic or disrupt the activities of endogenous hormones. Studies have linked endocrine disruptors to adverse biological effects in animals, giving rise to concerns that low doses of these chemicals may cause similar effects in human beings.

Question 10. Is there an established list of known endocrine disruptors?

Answer. At this time, FDA does not have an established list of endocrine disruptors. However, FDA uses all available resources in evaluating chemicals and their relevant (to dose) modes of actions. This is achieved using literature searches of FDA files and public information as well as computer-simulated toxicology programs which can predict the reproductive or teratogenic potential of a chemical. For instance, one resource FDA is aware of is EPA's draft list of 73 chemicals to undergo "Tier I" screening in the Endocrine Disruptor Screening Program (EDSP). The EPA list should not be construed, however, as a list of known or likely endocrine disruptors.

Question 11. Are there already alternatives to BPA and phthalates? Are these alternatives safer than what is currently being used? What science or studies exists into these alternatives?

Answer. With respect to food contact materials, there are non-phthalate plasticizers, including several citrate esters and a terephthalate ester, that are commercially available and approved by FDA for food contact use. Our data indicate that the alternate plasticizers and alternate cling wrap materials have already reduced significantly the consumer exposure to phthalates. Similarly, the use of BPA in polycarbonate drinking bottles and cups seems to have been largely replaced by a polyester plastic recently authorized for use by FDA.

The situation with BPA-containing epoxy resin can coatings is somewhat different in that there are no coating materials as suitable as the epoxy resins. Alternate coating materials approved by FDA are available, but none have the combination

of properties (adherence, flexibility, chemical resistance) that make epoxy coatings so useful and beneficial for preserving canned food from microbiological contamination.

Any alternative to BPA or phthalates would need to meet the same safety standard for use that the food contact materials containing BPA and phthalates must meet. FDA judges the safety of all food additives against the same safety standard of "reasonable certainty of no harm" and does not make judgments regarding whether one chemical that meets this standard is "safer" than another. The amount of data necessary to support the safe use of any alternatives will vary based on the properties and uses of those particular chemicals.

With respect to the use of BPA in medical devices, eliminating this chemical would require finding one or more chemicals that have the same beneficial characteristics as BPA but do not raise new biocompatibility or manufacturability issues. In fact, it is possible that there may not be an equivalent to BPA.

With respect to phthalates, there have been a number of other "esters" developed to replace DEHP as a vinyl plasticizer. Examples include long chain esters of citric acid (Citroflex™) and epoxidized soybean oil or other vegetable oils (Vikoflex™). However, the amount of research that has been conducted in animal and human studies of these vinyl plasticizers is quite small. Because the potential toxic effects of alternatives to phthalates require further study, we cannot conclude at this time that these alternatives are safer for use in medical devices.

Question 12. Do infants and children have the same immune and endocrine system as adults? Do studies take into account these differences?

Answer. Infants and children do not have the same immune or endocrine system as adults, especially in terms of functions. These systems in infants and children are considered immature; this simply means that their immune and endocrine systems do not function in an equivalent manner to that of adults. Some studies, such as multigenerational or chronic studies with an *in utero* exposure period, are designed to take into account these differences. Toxicologists recognize, however, that many uncertainties remain with regard to the relevance of laboratory animal development as compared to human development, the appropriate methods for testing, and the extrapolation of findings in rodents to humans. For many of the endpoints which have recently begun to be highlighted, such as neural and neurobehavioral developmental endpoints, many questions exist with regard to implications for human safety assessment.

Question 13. Have we seen many human studies on these chemicals? Is it even possible or ethical to conduct human studies?

Answer. There are only a few studies involving human exposure available. These studies are retrospective epidemiology studies and limited to certain parameters, for instance, studies have been conducted on miscarriage and BPA levels. However, as commented on in the CERHR expert panel review, none of the currently available studies is sufficient to make conclusions regarding BPA's toxicity in humans. The Center for Disease Control and Prevention's National Health and Nutrition Examination Survey has and will continue to test for levels of BPA in human biological fluids. FDA sees this effort as extremely helpful in determining the actual internal dose to BPA, which is useful in verifying assumptions with regard to exposure and safety assessment.

Question 14. Usually chemicals are tested one at a time. However, we come into contact with numerous chemicals every day. Do these studies simulate real world exposures and what is the best way to test chemicals?

Answer. The issue with regard to mixtures and safety assessment is one that is extremely difficult to address, but occurs in the real human experience. Toxicologists know that chemicals involved in the same pathways may act additively, synergistically, or may inhibit one another. However, for risk assessment purposes, chemicals are normally tested individually to avoid data interpretation difficulties that may result from metabolic and toxicological interactions with other chemicals. This is usually done at much higher doses than human exposures for the comparison of effects observed in animal testing to the human estimated exposure (margin of safety). Testing chemicals at dose levels simulating "real world" exposures would require an extremely large number of animals to determine an effect that was not considered a random or chance event. Basing any conclusions on random or chance events relating to potential toxicity may give a false sense of safety. Considering all possible exposures to chemicals with known modes of actions is an insurmountable challenge based on current science. In addition, as is the case with BPA, environmental or dietary compounds such as phytoestrogens, which are naturally present in soy-based food products, may also be potential confounders.

Question 15. What about workers who are in the plants that manufacture phthalates and BPA. Are protections in place to make sure that they aren't unnecessarily exposed?

Answer. While toxicological data and analyses that have been developed by FDA may be useful in assessing the effects of exposure in the workplace (and vice versa), issues related to workplace safety are under the regulatory purview of the Occupational Safety and Health Administration. That agency, rather than FDA, would be better positioned to answer this question.

RESPONSE TO WRITTEN QUESTIONS SUBMITTED BY HON. JOHN F. KERRY TO NORRIS E. ALDERSON, PH.D.

Question 1. In light of the results of the 2007 assessment by the Center for the Evaluation of Risks to Human Reproduction and last month's draft brief from the National Toxicology Program, what actions is FDA taking to ensure the safety of products that contain BPA? Why is FDA allowing consumer products—particularly children's products—that contain BPA to stay on the market?

Answer. Commissioner of Food and Drugs Andrew C. von Eschenbach, M.D. has formed an Agency-wide BPA Task Force 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, and is actively reviewing NTP's Draft Brief.

Members of the Task Force have met with NTP staff to discuss their findings and better understand the underlying data. Also, staff of FDA's NCTR is discussing with NTP additional research needs relating to 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 BPA Task Force is conducting an inventory of all products regulated by FDA's food and medical products centers and is reviewing other potential routes of exposure. Additionally, the Task Force has met with representatives of product manufacturers to better understand manufacturing and chemistry issues. Finally, the Task Force is considering what recommendations for further laboratory studies or other research may be appropriate.

The NTP has stated that its Draft Brief on BPA is not a quantitative risk assessment, nor does it supersede risk assessments conducted by regulatory agencies. The report stated that more research is needed to better understand the health implications of BPA exposure. Although FDA's 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.

Question 2. In your written testimony, you note that FDA continues to monitor the safety of phthalates and BPA. How much information is required before FDA will make a decision that exposure to these chemicals is not safe? Are there established decision points for reevaluation?

Answer. FDA's re-evaluation of any food additive involves a determination of whether the permitted use of that compound continues to meet the safety standard. That is the primary decision point for FDA to take action. There is no minimum amount of data necessary to reach that decision point but the data underpinning such a decision must be relevant to the safety assessment of the chemical. FDA's current consideration of the data on BPA follows.

Information exists indicating the possibility of concern for humans exposed during development. That possible concern includes developmental toxicity effects (neural and behavioral effects, prostate gland, and early onset of puberty in females) and a possible predisposition for cancer (mammary and prostate glands) later in life. The data generating these concerns are rodent data and contain many uncertainties and limitations. For example, regarding the conclusion of a predisposition of cancer, for both endpoints, the NTP stated that "The evidence is not sufficient to conclude that bisphenol A is a rodent [mammary/prostate] gland carcinogen or that bisphenol A presents a [breast cancer/prostate] hazard to humans."

FDA takes the NTP and its expert panels' conclusions seriously and our Task Force is currently reviewing these data as they relate to the safety assessments of BPA-containing products that are regulated by FDA. The Agency's established decision points in this re-evaluation are to consider the information that has indicated a concern and report those findings with recommendations to the Commissioner for appropriate action. FDA's activities with regard to BPA will be conducted using public peer review and the FDA Science Board. At FDA's request, the FDA Science

Board, which is an independent advisory body to FDA on scientific issues, is forming a subcommittee on BPA to undertake scientific peer review of the Task Force report. Part of that peer review process will be to hold a public meeting to accept input and comments from the public. The full Science Board will receive the findings of the Subcommittee during its fall meeting.

With regard to phthalates, CFSAN's Phthalate Task Group is evaluating current use levels and, based on the information gathered, will consider what action may be necessary to establish a more realistic exposure estimate. Any actions necessary to modify the existing regulations to reflect current known practices will be pursued, as appropriate. Should FDA's updated assessment indicate a safety concern, appropriate regulatory actions will be taken to protect consumers.

Question 3. News reports have indicated that the FDA relied exclusively on a handful of industry-funded studies of the low-dose effects of BPA, in the face of contrary evidence from dozens of scientific studies. Is this accurate?

Answer. FDA's position on BPA is based on the consideration of hundreds of studies and is *not* derived solely from the review of the two industry-funded studies. However, FDA has concluded that these two studies are pivotal to the safety assessment of BPA, due to the design of the studies and the quality of the data. While we have used these studies in determining the current "no observed effect level" (NOEL) for BPA, this is not the same as stating that our position is entirely dependent on consideration of only these two studies.

The two rodent studies that were considered pivotal were sponsored by the American Plastics Council and the Society of the Plastics Industry and were conducted by RTI International, Research Triangle Park, North Carolina. The studies were conducted to address questions concerning possible low-dose effects of BPA on endpoints that were of concern at that time. The industry briefed FDA and our European counterparts on the two studies during the planning and execution phases. These studies were considered pivotal in our review of the existing data for a number of reasons, including the following: (1) they were conducted in a manner that CFSAN's Office of Food Additive Safety would recommend to a stakeholder seeking an approval for a new use (*i.e.,* they follow Agency guidelines) and included additional protocol considerations allowing for the examining of issues that were controversial to BPA at the time planned; (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. These studies have been given more weight in FDA's evaluation of BPA, compared to publications in the public literature that examine the same endpoints, because these publications often lack details and supporting data that would allow Agency scientists to make an independent evaluation of the underlying data. 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 failure to use multiple or correctly spaced doses in the experimental protocol, and the route of administration.

Question 4. Do your agencies require labeling of consumer products that contain BPA or phthalates? Is there any control over current voluntary labeling of products as "BPA-free" or "phthalate-free"?

Answer. FDA does not require such labeling. Because FDA has not made a determination that BPA or phthalates, under current conditions of use, are unsafe, we do not believe that labeling for the presence of these chemicals would provide consumers with meaningful information on the safety of the products. Pursuant to our authority under the Federal Food, Drug, and Cosmetic Act, if FDA determined that a water bottle or other product containing BPA was in fact not safe, we would not address it through labeling; rather, we would take action to restrict or possibly disallow its use.

Manufacturers are permitted to voluntarily label products as "BPA free" or "Phthalate free" so long as the labeling statements are truthful and not misleading.

Question 5. Can you please explain the different roles for FDA, CPSC and EPA in the study and regulation of phthalates, BPA and other endocrine disrupting chemical compounds? Do the agencies share data and information?

Answer. FDA is the agency responsible for the safety of food and medical products, and this jurisdiction includes food containers and packaging (food contact materials). Although BPA itself is not considered a food additive, it is present as an impurity in polycarbonate plastics and epoxy-based resins and was considered as part of FDA's overall review of BPA-containing food contact materials. Similarly, phthalates are considered as part of FDA's review of food contact materials when

they are added to food contact polymers to help soften them and make them more pliable (*i.e.,* they act as plasticizers).

The Consumer Product Safety Commission (CPSC) is responsible for the safety of consumer articles that would not fall under the jurisdiction of the FDA. For example, although baby bottles and nipples would fall under the jurisdiction of FDA, the safety of baby pacifiers or toys would fall under CPSC. EPA is responsible for the effect of chemicals on the environment as a result of their manufacture, use, and disposal.

FDA, CPSC, and EPA work closely in areas where our jurisdiction converges. A recent example of such cooperation is the response in 2006 to elevated lead levels in soft-sided polyvinyl chloride (PVC) lunchboxes, where FDA and CPSC shared data and information. FDA was concerned about the potential for lead migrating into food held in the PVC lunchboxes while CPSC was concerned about potential exposure of children to the lead by touching the PVC or by putting parts of the PVC lunchbox in their mouths.

Memoranda of understanding have been developed over the years to help facilitate cooperation between FDA and both CPSC and EPA.

Question 6. Do we know what levels of BPA and phthalates are safe for human (particularly child) consumption?

Answer. Ordinarily, FDA uses the term "acceptable daily intake" (ADI to define the estimated maximum amount of a food additive to which individuals in a population may be exposed daily over their lifetimes without an appreciable health risk. These levels are determined by examining endpoints from which the NOEL or no observed adverse effect level (NOAEL), if appropriate, is calculated in animal studies. However, since BPA is an impurity and not a food additive, FDA considers margin of safety (MOS) more appropriate in evaluating the safety of BPA. The MOS is compared to the typical uncertainty factors used for the appropriate endpoint in deeming if the substance is safe for the expected exposure.

CFSAN's typical uncertainty factors are 10 for intraspecies variability and 10 for interspecies variability for reproductive or developmental effects that are reversible (which is the observation at the NOEL for BPA). For systemic toxicity, exposure in the applicable studies is less than chronic; therefore, an additional factor of 10 is used to extrapolate from subchronic to chronic exposure. Using this approach, the Agency has determined adequate safety margins for both infant and adult exposure to BPA, based on the NOELs identified in Tyl. *et al.* (2002, 2008) rodent studies. The lowest NOEL in both studies was 5 mg/kg bw/day, based on the endpoint of systemic toxicity. FDA's task force is currently examining the additional endpoints identified in the recently released draft documents as they relate to the current exposure and the previously examined and referenced toxicity studies. Should FDA's updated assessment indicate a safety concern, appropriate regulatory actions will be initiated to protect consumers.

FDA's approach to phthalates is similar to BPA. As noted in the response to your earlier question, CFSAN's Phthalate Task Group is currently evaluating current use levels of phthalates in food contact materials and based on the information obtained, FDA will reassess the safety of food contact materials containing phthalates. Should FDA's updated assessment indicate a safety concern, appropriate regulatory actions will be initiated to protect consumers.

RESPONSE TO WRITTEN QUESTIONS SUBMITTED BY HON. MARK PRYOR TO DR. MARILYN L. WIND

Question 1. According to my information, CPSC has never done a comprehensive study on the effects of all phthalates. Why has CPSC not undertaken a thorough study? In light of recent reports, does CPSC intend to do a full review of possible effects of phthalate exposure?

Answer. CPSC's primary interest in phthalates has been exposure levels resulting from the mouthing of children's products, especially pacifiers, teethers and rattles. In this regard, the CPSC conducted comprehensive studies of the two phthalates (DINP and DEHP) that were used in children's products intended to be mouthed. In regulating a product under the Federal Hazardous Substances Act (FHSA), the CPSC must consider the toxicity of a product and the consumer's exposure to that product under reasonably foreseeable handling and use. Accordingly, the CPSC prioritizes its research work related to phthalates by concentrating on those consumer products under the agency's jurisdiction where there is a concern about such toxicity and exposure.

Foods and cosmetics would be the primary source of human exposure from phthalates other than DINP and DEHP, and those products fall under the jurisdic-

tion of the Food and Drug Administration (FDA). Since manufacturers have removed DINP and DEHP from children's products that are intended to be mouthed, the CPSC has now initiated a study of substitutes that may be used to replace these phthalates. Additionally, CPSC staff continues to monitor the scientific literature on phthalates, including new data expected from the comprehensive National Research Council study on all phthalates.

Question 2. The "low-dose hypothesis" claims that exposure to extremely low levels of certain substances could cause adverse health effects in humans. Some have criticized existing studies and reviews for looking at only high dosage exposure. Have any of the governmental reviews done by CPSC taken into account studies showing adverse health effects from low-dose exposure to BPA?

Answer. 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) stated that diet accounts for 99 percent of human exposure. Accordingly, primary jurisdiction for BPA falls under the FDA. The CPSC has not conducted studies on adverse health effects from low-dose exposure to BPA and would defer to the authority and expertise of the FDA in this case. It should be noted that the NTP has released a comprehensive peer-reviewed report on this subject.

Question 3. The results of studies into the potential health effects of BPA and phthalates conducted by the government, industry, and some in academia seem to vary quite widely in their results. How would you explain these differences? Does the CPSC take into account the safety of these chemicals when rendering its opinions?

Answer. With regard to Bisphenol A (BPA), there are a large number of studies giving very varied results. Since the NTP Center for the Evaluation of Risk to Human Reproduction conducted a comprehensive Peer Review Panel of all the literature, and since BPA exposure results primarily from products under FDA jurisdiction, the CPSC has deferred to the NTP and FDA in the evaluation of BPA.

With regard to phthalates, the European Union (EU) and the CPSC reached different conclusions in their risk assessments on DINP. While the European Union evaluated other phthalates as well, the CPSC did not since the primary exposure to children was from DINP. EU scientists and CPSC scientists discussed the differences in their respective risk assessments of DINP. When the CPSC was examining the health effects of DINP, it convened a Chronic Hazard Advisory Panel (CHAP), which is a panel of seven independent scientists recommended by the National Academy of Sciences, to review the studies and advise the Commission on its findings. The report from the CHAP, as well as the subsequent staff hazard and risk assessment, was based on a review of all available scientific studies. At the time of the CHAP, the results from the Commission behavioral observation study were not available. However, the CHAP concluded that there was no concern for infants who mouthed toys containing DINP for less than 75 minutes per day. The CPSC's behavioral observation study indicated that children's daily mouthing time of such toys is significantly less than that. Staff, therefore, concluded that there was not a risk of injury to children from such exposure. The EU risk assessment was exactly the same as the CPSC risk assessment, but the EU assumed an exposure that was larger than 75 minutes per day, without doing any behavioral studies to substantiate such an assumption. CPSC's study showed that such an assumption was not justified.

Thus, the CPSC staff's risk assessment was based upon exposure data developed in a well conducted behavioral observation study whereas the EU risk assessment was based upon an assumed exposure that was many fold higher than that observed in the CPSC study. As indicated previously, the FHSA requires that the Commission make a determination of risk based upon both hazard and exposure and in that way assess the safety of products when making its decisions.

Question 4. Please explain the significance of low-dose exposures to BPA and how it relates to the traditionally held belief of "the dose makes the poison"?

Answer. As noted above, BPA falls under the primary jurisdiction of the FDA since diet accounts for 99 percent of human exposure. Accordingly, the CPSC defers to the expertise and authority of the FDA with regard to low-dose exposures to BPA.

Question 5. How is the average person exposed to phthalates? What is the best way to reduce exposure to phthalates? Please explain the significance of phthalate mixtures.

Answer. For products under CPSC's jurisdiction, the agency has been primarily concerned about phthalate exposure from the mouthing of children's products, especially pacifiers, teethers and rattles. In this regard, the CPSC has conducted comprehensive studies of the two phthalates, DINP and DEHP, where exposure to children from their use was a matter of concern. The staff's risk assessment also consid-

ered "background" exposures from phthalates in addition to DINP; however, because most of the products studied by CPSC staff contained that single phthalate, the risk assessment focused on DINP. Most exposures from other phthalates were from food and other sources not regulated by the CPSC. As noted above, manufacturers subsequently removed DINP and DEHP from children's products that are intended to be mouthed, and the agency's current focus is on studying exposure to possible substitutes that may be used to replace these phthalates.

Question 6. What are endocrine disruptors and how do they affect us?

Answer. The term endocrine disruptors does not have a precise definition. It has been used to define endocrine active substances in animals as well as chemicals that bind to an estrogen or androgen receptor or are positive in other *in vitro* or *in vivo* tests. The relevance to human risk of positive results in these assays has not been determined and is still under considerable discussion by the scientific community at large.

Question 7. Is there an established list of known endocrine disruptors?

Answer. CPSC staff does not know of any such list nor is the term well defined.

Question 8. Are there already alternatives to BPA and phthalates? Are these alternatives safer than what is currently being used? What science or studies exists into these alternatives?

Answer. The scientific community does not know all the alternatives that are being used for phthalates. When switching from phthalates, manufacturers can continue to use polyvinyl chloride (PVC) containing a plasticizer other than a phthalate or they can use a completely different plastic than PVC. As noted above, the CPSC has recently initiated a study of phthalate substitutes. This study will determine what is known about the toxicity of some of these alternatives. In order to use a chemical in a consumer product, manufacturers are not required to do any particular toxicity testing. However, the FHSA requires that a manufacturer provide cautionary warning on products that meet the definition of a hazardous substance. The implementing regulation provides test methodologies for a manufacturer to test their products to determine if they meet the definition and requires warnings for the safe use and storage of the product. While manufacturers may do such testing for household chemical products, often the chemicals used in other types of consumer products have no toxicity information; the chemical may be more, less or equally toxic to the chemical it is replacing. Lack of toxicity data does not mean that the chemical is non-toxic; it just means the toxicity profile of the chemical is unknown. The CPSC does not have pre-market clearance authority for a product containing a new chemical or for a new use of an existing chemical. The Environmental Protection Agency (EPA) has been given those authorities under the Toxic Substances Control Act.

Question 9. Do infants and children have the same immune and endocrine system as adults? Do studies take into account these differences?

Answer. Depending upon the age of the infant/child and the particular system under consideration, there may be differences which would make the infant/child more or less sensitive than an adult. In some cases studies take these differences into account by using immature animals.

Question 10. Have we seen many human studies on these chemicals? Is it even possible or ethical to conduct human studies?

Answer. Intentional testing of chemicals for toxicity in humans is generally not done, precisely for the reason stated; it is not ethical. Epidemiological studies are sometimes conducted in which exposures are measured or estimated and the occurrence of adverse effects are recorded. Epidemiology is sometimes a powerful tool for assessing the toxicology of chemicals, but studies in humans are generally difficult, time-consuming and expensive. For example, many of the potential effects are ones that might occur after long-term exposure, may not be apparent for many years, and may have effects that are the same as those from other chemicals to which a person is exposed. There are a limited number of studies in which metabolites of phthalates have been looked for in the urine of humans. There are few epidemiological studies that exist and the effects in humans have not been clearly demonstrated.

Question 11. Usually chemicals are tested one at a time. However, we come into contact with numerous chemicals every day. Do these studies simulate real world exposures and what is the best way to test chemicals?

Answer. The toxicological effects of chemicals, in general, are tested one at a time because testing more than one chemical at a time would confound the results and it would be impossible to determine which of a group of chemicals tested together was responsible for the toxicologic endpoint. Because of the nearly limitless combinations of potential chemical exposures in the world, it is simply not possible to

test mixtures in most cases. In certain cases, such as household chemical products, where one particular product contains a mixture of chemicals, the product generally is tested as a whole in the United States to determine appropriate classification and labeling. Further, if appropriate data are available for a given exposure scenario, a risk assessment could consider information about more than one chemical to determine the overall risk. The "science" of conducting risk assessments for mixtures is very new.

Question 12. What about workers who are in the plants that manufacture phthalates and BPA. Are protections in place to make sure that they aren't unnecessarily exposed?

Answer. CPSC's jurisdiction does not cover chemical exposures in the workplace. The Occupational Safety and Health Administration (OSHA) has jurisdiction over worker exposure to chemicals.

RESPONSE TO WRITTEN QUESTIONS SUBMITTED BY HON. JOHN F. KERRY TO DR. MARILYN L. WIND

Question 1. In your written testimony, you explain the CPSC's 2003 decision to deny the request to ban polyvinyl chloride (PVC), which contains phthalates. Has any new evidence surfaced since 2003 that would lead you to reconsider that decision?

Answer. No new scientific evidence has surfaced since 2003 that would lead CPSC staff to recommend to the Commission that it reconsider its decision to deny the request to ban polyvinyl chloride which contains phthalates.

Question 2. Do your agencies require labeling of consumer products that contain BPA or phthalates? Is there any control over current voluntary labeling of products as "BPA-free" or "phthalate-free"?

Answer. At present, the CPSC does not require labeling of products containing either phthalates or BPA. Under CPSC's governing statutes, the Commission has the authority to require labeling only if a product is determined to be a "hazardous substance." CPSC's statutes are risk-based, not "hazard-based." That is to say, the product in question must actually pose a risk of substantial illness or injury, not simply contain a potential toxicant. The FTC has jurisdiction over the labeling of products that make claims such as "BPA-free" or "phthalate-free."

Question 3. Can you please explain the different roles for FDA, CPSC and EPA in the study and regulation of phthalates, BPA and other endocrine disrupting chemical compounds? Do the agencies share data and information?

Answer. Each regulatory agency has specific jurisdiction which is defined in their laws and regulations. FDA generally has responsibility over food, drugs, and cosmetics. EPA has broad authority over the manufacture of chemicals and the implementation of new uses for existing chemicals. The CPSC has responsibility generally over consumer products and their potential for substantial injury or illness in reasonably foreseeable use scenarios. In addition to defining their authority, these agencies' laws and regulations restrict certain types of information that can be shared outside each agency. For information that is not restricted, agency scientists often share scientific information, develop needed data together, and participate on interagency groups such as the National Toxicology Program and its committees and then process the information within their own statutory or regulatory framework.

Question 4. Do we know what levels of BPA and phthalates are safe for human (particularly child) consumption?

Answer. CPSC staff developed an Acceptable Daily Intake (ADI) for the amount of the phthalate DINP that could be ingested on a chronic basis and not result in an adverse health effect. CPSC staff has not developed ADI's for BPA or other phthalates since there were no exposures to these chemicals from consumer products under the agency's jurisdiction which would indicate that a determination of an ADI was warranted.

RESPONSE TO WRITTEN QUESTIONS SUBMITTED BY HON. DANIEL K. INOUYE TO JOHN PETERSON MYERS, PH.D.

Question 1. What research is being done to determine the effects these chemicals have on wildlife?

Answer. Wildlife research has received much less attention than potential effects of bisphenol A and phthalates on laboratory animals and on humans. There is very little funding available to pursue this line of inquiry.

There is no published literature on phthalates and wildlife nor am I aware of any active research program currently studying this issue. I am aware of one unpublished study, carried out by Dr. Louis Guillette and his students (University of Florida, Gainesville), in collaboration with the U.S. Centers for Disease Control, finding unexpectedly and extremely high levels of phthalates in alligators living in the wild in Florida. Alligators sampled in the Everglades contained average levels of the phthalate MEHP in their urine of almost 100 parts per million. Because the CDC did the chemical analysis, and re-did their assay once these exceptional values were discovered, the data are credible. That is an extraordinarily high level to encounter in any non-experimental organism. Phthalate levels from alligators in central Florida are not quite as high, but still a cause for significant concern. The researchers believe that the source of exposure is the use of phthalates as stabilizers in herbicides being used to control aquatic vegetation. If that is the case, these levels might be quite widespread. Research examining the extent of phthalate contamination in wild animals and ascertaining the consequences should be a high priority.

Two extensive reviews summarizing research on bisphenol A and wildlife have been published within the past 12 months:

Crain, D., *et al.,* 2007. An ecological assessment of bisphenol-A: Evidence from comparative biology. *Reproductive Toxicology* 23:225–239.

Canadian Ministry of the Environment. 2008. Draft Screening Assessment for Phenol, 4,4'-(1-methylethylidene)bis- (80-05-7). Available for download at: *http://www.ec.gc.ca/substances/ese/eng/challenge/batch2/batch2_80-05-7.cfm*.

Because of the paucity of funding, there is no comprehensive effort in the U.S. to gather information about the effect of BPA on wildlife. Research dollars from the Federal Government into these issues have declined dramatically over the past decade. Almost all of the work underway is on aquatic organisms.

In the U.S., the United States Geological Survey laboratory in Columbia, Missouri, is studying BPA and its effects on fish. Dr. Don Tillett and Dr. Kathy Richter are the principal scientists.

In Japan, Dr. Koji Arizono at the University of Kumamoto is conducting research on BPA and fish.

In Germany, Dr. Jörg Oehlmann at Johann Wolfgang Goethe University, Frankfurt, is the lead researcher on effects of BPA on marine snails.

Question 2. What are the known effects of these harmful plastic chemicals on wildlife?

Answer. To my knowledge, there are no published papers in the modern literature on phthalates and wildlife. This is extraordinary given the widespread use of phthalates as inert ingredients in pesticides. Given what is known about the reproductive harm caused by phthalates in laboratory animals, if the unpublished data from Guillette's lab (above) are representative, then widespread damage is likely to be occurring.

Documented effects of BPA on wildlife are varied but much more needs to be learned. As summarized in the Canadian review (reference above), BPA at high doses is acutely toxic to aquatic organisms and considered highly hazardous. Low concentrations of BPA are sufficient to a range of adverse effects, especially at sensitive stages of development. These effects include feminization of male fish, delayed development of aquatic invertebrates, 'super-feminization' of marine snails (leading to death of females), delayed emergence and mouthpart deformities in insects.

RESPONSE TO WRITTEN QUESTIONS SUBMITTED BY HON. MARK PRYOR TO JOHN PETERSON MYERS, PH.D.

Question 1. Some have pointed out the preponderance of studies showing the safety of these and other chemicals used in consumer products. It would seem that there are significantly less studies purporting the harm or risk of these chemicals. How do you respond to these criticisms?

Answer. The reverse is true. Many more studies have been published that find adverse effects resulting from low levels of exposure. This pattern itself has been published in the peer-reviewed literature: vom Saal, F. and C. Hughes, 2005. An Extensive New Literature Concerning Low-Dose Effects of Bisphenol A Shows the Need for a New Risk Assessment. *Environmental Health Perspectives* 113:926–933. In an extensive review of the literature, they showed that over 90 percent of government-funded studies of low-dose effects found adverse effects. An update of their tally through July 2007 shows that 166 out of 195 (85 percent) studies published on the effects of BPA at low doses find adverse consequences. Out of 14 industry-funded studies to date, none have found adverse effects. Out of 181 government-funded studies, 166 (92 percent) have found adverse effects.

There is a vital difference between industry-funded studies and those funded by government (mostly by NIH). The NIH-funded studies must meet the highest standards of scientific rigor simply to get funded. They use highly sophisticated and sensitive assays that incorporate the latest knowledge from medicine, endocrinology, reproductive development, neurobiology, etc. The scientists, to be competitive in this day and age of shrinking research budgets, must be among the best in the world. Their work focuses not only on the structural changes that are caused, but also on the genetic mechanisms underlying those changes. That is key, because BPA's principal mode of action is through altering the expression of genes.

In contrast, industry-funded studies are using techniques dating to the middle of the last century, literally. They measure gross changes in anatomy and weight. And they do so poorly, because they usually involve multiple technicians with limited training to carry out the measurements. This use of multiple technicians introduces variability that makes it more difficult for them to find significant results.

Plastic industry representatives are critical of the sample sizes of NIH-funded research, and use that criterion to exclude many excellent studies. This is a false criticism. NIH requires scientists to use as few animals as necessary. NIH-funded scientists respond to this requirement in two scientifically-tested ways. First, they perform a statistical power analysis which allows them to calculate, based on preliminary results, how large a sample will be required to achieve a given level of significance, if the preliminary results are valid. Second, they either use only one technician for crucial measurements, reducing variability, or they carefully examine inter-observer variability, and factor that into their analysis. These are standard NIH procedures.

Importantly, the estimate of statistical significance factors in its calculation the sample size of the study. A small sample size requires a bigger difference between controls or experimentals, or less variance, or both, to achieve a given level of significance. Insisting upon an arbitrary sample size is not scientific and ignores basics statistics.

Industry often points to the fact that its experiments follow "Good Laboratory Practices" or GLP. This says nothing about the quality of the science, only that they followed certain standards of record-keeping that were established after massive fraud was found in the results of contract laboratories.

The most recently published study from an industry laboratory purporting to find no effect of BPA on the developing mouse prostate is a good example of how GLP does not translate into good science:

Tyl, R., *et al.,* 2008. *Toxicological Sciences,* in press. This study's major failure is its inappropriate use of a positive control. Scientists use positive controls to demonstrate their competence at performing the experiment. A positive control is performed by exposing a group of animals to an agent known to cause an effect. In this case, Tyl *et al.*'s published data show that the strain of mice they used required a high dose of their positive control, estradiol. It would not respond to a low dose. If the strain wouldn't respond to a low dose of the positive control, it couldn't be expected to respond to a low dose of bisphenol A, which typically, for this type of effect, is 100 to 10,000 times less powerful than estradiol. Another weakness in this study was the choice of which positive control to use. Estradiol was a highly unusual choice, which means there is no scientific literature against which to compare the results of the experiment and help understand why it required such high doses.

Question 2. How precautionary should we be when the weight of evidence seems to show these chemicals are safe?

Answer. The weight of the evidence shows that bisphenol A is not safe. We should immediately begin phasing out uses that lead to human exposure. The strongest evidence is for developing organisms. Therefore the highest priority should be placed on measures that will reduce exposures for pregnant women, infants and children. Some evidence also indicates risk for men with prostate cancer (it interferes with the standard medical treatment for prostate cancer). We should also invigorate investments in 'green chemistry' to identify safe replacements.

Question 3. Please explain the significance of low-dose exposures to BPA and how it relates to the traditionally held belief of "the dose makes the poison"?

Answer. Bisphenol A is a synthetic sex hormone. Endocrinologists have known for years that *all* hormones can have different effects at different doses. This is called a 'biphasic response' or a 'non-monotonic dose response curve.' It is well established in the literature of medical endocrinology. This means that the effects seen at one dose, for example a high dose, may be completely unrelated to other effects seen at low doses. With bisphenol A, at very high levels it is toxic. For example, the experiments used to establish the current FDA and EPA standards showed that at relatively high doses (50 mg/kg/day) it causes weight loss in mice. At low doses, how-

ever, BPA turns on genes that are responsive to estrogen. These responses and their effects are very different from the ones seen at the levels at which BPA is toxic.

This means that tests of the effects of BPA at high doses can't be used to predict what will happen following a low-dose exposure. It directly contradicts a fundamental assumption of toxicology that "biological effects increase as the dose increases." At one dose level BPA will alter the expression of one set of genes while at another it will affect a different set. And at high levels it is overtly toxic, so the mechanism of impact is not through alteration of gene expression.

Question 4. How is the average person exposed to phthalates? What is the best way to reduce exposure to phthalates?

Answer. Exposures to phthalates come from many, indeed ubiquitous sources, although the type of phthalate varies significantly depending upon the type of product or use. Common sources of exposure include leaching from PVC plastic, dermal absorption of phthalates used in cosmetics and personal care products, exposure to phthalates in dust generated by abrasion of phthalate containing products, including carpeting and building materials.

Phthalate exposure can be reduced by avoiding products that contain them. Unfortunately, products are not required to identify their phthalate content in labels. Some do. Two general rules of thumb: do not heat (including microwave) food or drinks in plastics; avoid unnecessary personal care products.

Question 5. Please explain the significance of phthalate mixtures.

Answer. Research that has been published over the past 5 years has drawn attention to the fact that mixtures of contaminants can have effects even when each of the components of the mixture is at a dose at which, by itself, it can cause no harm. Work by Dr. Earl Gray (U.S. EPA) has extended these basic findings into research on phthalates. He has shown that a mixture of different phthalates, each one at a level insufficient to cause harm, can cause dramatic harm in exposed animals.

This is important because current regulatory assessments of phthalates are all evaluate phthalates one-by-one. No accounting is made for the fact that virtually all people are exposed to multiple phthalates continuously.

Question 6. What are endocrine disruptors and how do they affect us?

Answer. Endocrine disruptors are chemical contaminants that interfere with hormone action. There are multiple mechanisms. The best studied involve altering the expression of genes under the control of hormones, either directly or indirectly. Some endocrine disruptors, for example BPA, mimic the action of hormones. BPA is an estrogen mimic. It causes effects that resemble the effects of adding estrogen. Other endocrine disruptors interfere with the action of hormones. For example, phthalates interfere with testosterone and other androgens. They are deemed 'anti-androgens.'

Interfering with hormone action can cause adverse effects by altering the timing and pattern of gene expression. During fetal development, for example, it is imperative that gene expression follow a normal pattern; otherwise development can be adversely affected.

Initially scientists believed that compounds like bisphenol A were 'weak' estrogens. That was because they were focused on only one mechanism of action. In the last 5 years research has revealed that BPA and similar compounds can be just as powerful as estrogen.

Question 7. Is there an established list of known endocrine disruptors?

Answer. There have been several efforts to compile lists of endocrine disruptors, but none incorporate the most recent research.

Here are several existing lists:

IEH. 2005 Mar. Chemicals purported to be endocrine disrupters. A compilation of published lists. Leicester, UK: MRC Institute for Environment and Health. (Web Report W20). Available at: *http://www.silsoe.cranfield.ac.uk/ieh/pdf/w20.pdf.*

> Abstract: [A total of 966 compounds or elements were identified as having been suggested to be established or potential endocrine disrupters (EDs). The list is based on the BKH (2000) report; Environmental Defense—Scorecard sources; the German Federal Environment Agency; the UK Institute for Environment and Health; the California EPA; the Japan Chemical Industry Ecology-Toxicology & Information Center and other publications. Online databases Medline, Biosis, Embase, NTIS, ToxNet, SciSearch, Pascal and CA Search were searched during the period Jan 2000-Jan 2002. Chemicals are grossly classified into *General Anthropogenic* (alcohols & glycols; aromatic hydrocarbons; anilines & derivatives; benzene & derivatives; benzophenones and derivatives; biphenyls and metabolites; dioxins and metabolites; diphenyl derivatives; diphenyl ethers; furans and metabolites; naphthols & naphthalenes; phenols and derivatives;

phthalate esters and derivatives; siloxanes; styrene and derivatives; miscellaneous), *Biocides* (carbamates; fungicides; herbicides; organochlorines; organophosphates; pyrethroids; miscellaneous), *Biogenic* (anthraquinones; flavanones; isoflavonoids; lignans; phenolic acids; plant-derived substances; vitamins; miscellaneous), *Pharmaceuticals, Inorganic & Organometals and Consumer Products.* There are 6 tables corresponding to these categories, giving the chemical name, CAS number, chemical group and/or use, references (mostly from previous compilations), and Notes (type of endocrine disruption activity, and/or level of concern or (un)certainty). Five pages of references follow.]

European Commission. Endocrine Disrupters website. *http://ec.europa.eu/environment/endocrine/strategy/substances_en.htm.* This website links to the documents listed below:

DHI. 2007 May. Study on enhancing the Endocrine Disruptor priority list with a focus on low production volume chemicals. Revised report to European Commission DG ENV. ENV.D.4/ETU/2005/0028r. 252 pp. *http://ec.europa.eu/environment/endocrine/documents/final_report_2007.pdf.*

Wrc–NSF. 2002 Nov. Study on the scientific evaluation of 12 substances in the context of endocrine disrupter priority list of actions. 613 pp. *http://ec.europa.eu/environment/endocrine/documents/wrc_report.pdf.*

BKH–RPS. 2002 Nov. Study on gathering information on 435 substances with insufficient data. 279 pp. *http://ec.europa.eu/environment/endocrine/documents/bkh_report.pdf#page=1.*

BKH Consulting Engineers, TNO *Nutrition and Food Research.* 2000 Nov 10. Toward the establishment of a priority list of substances for further evaluation of their role in endocrine disruption. Final Report (incorporating corrigenda to final report dated 21 June 2000).: European Commission DG ENV. M0355008/1786Q/10/11/00. PDFs (16 files) available at *http://ec.europa.eu/environment/endocrine/strategy/substances_en.htm,* and also available at: *http://europa.eu.int/comm/environment/docum/01262_en.htm* (scroll down).

Abstract: [A list of 564 chemicals (including metals) (see Annexes 9 and 10) classified as "manmade" were compiled from other endocrine disruptor lists and classified as follows: 74 with high-production volume; 51 highly persistent; and 29 metals. The 146 chemicals discussed in the Annexes 6, 7, 12 and 13 refer to these three groups combined; the remainder are discussed in Annex 8. For extensive references see Annexes 9 and 11. Chemicals listed in table 3–6 are the same as those covered by Annex 14.]

Question 8. Are there already alternatives to BPA and phthalates? Are these alternatives safer than what is currently being used? What science or studies exists into these alternatives?

Answer. There are alternatives for many uses. For example, manufacturers have already brought to market plastic baby bottles that are not made from polycarbonate, the plastic based on BPA. One of the replacements is based upon a different type of chemistry that by definition is vastly less likely to leach anything even under conditions of stress. That is because of the nature of the chemical bonds. The bonds that bind BPA into polycarbonate are weak and dissolve readily. The bonds that bind polyether sulphone are exceedingly resistant to degradation. By definition they will be safer than BPA. Glass baby bottles are much safer too.

One of the most problematic of replacements is for the use of BPA as an epoxy resin to line food cans. There is no perfect substitute available for this lining. However, Japanese manufacturers have found a way to reduce BPA leaching by 95 percent. And some manufactures of baby formula have decided that they don't need to use cans at all. Instead they put the formula in cardboard containers. These are available in the U.S. and Japan.

Question 9. Do infants and children have the same immune and endocrine system as adults? Do studies take into account these differences?

Answer. The fetus, infants and children are developing into adults. As they develop, all their physiological, neurological and immune systems are maturing. That has two important implications for exposure to endocrine disruptors. First, their developing systems are responding constantly to hormonal signaling that can be disrupted by endocrine disruptors. And the consequences of that disruption, because it alters how development is unfolding, can have life long consequences. Those developmental processes are already completed in adults, so they are not vulnerable in the same way. Second, fetuses and the young do not produce all the enzymes that adults produce. Some of these enzymes are essential for detoxifying toxicants that

get into the blood stream. Without a mature set of enzymes, fetuses and the young are less able to defend themselves.

This is particularly relevant to BPA. The enzyme that detoxifies BPA in mammals, including people, is produced at much lower levels in the young. That makes the young more vulnerable to the same exposure. It is also part of some 'inside baseball' arguments over toxicity testing in BPA. Industry argues that because most human exposure to BPA is oral, only oral tests on animals are relevant. This criterion would eliminate some of the most striking low-dose results, which used injection or subcutaneous implants. However, these experiments were designed to mimic how a fetus experiences BPA. From the perspective of the fetus, it doesn't matter how the BPA gets into its mother's bloodstream. The National Toxicology Program in its review of the 'expert panel' assembled by the Center for the Evaluation of Risks to Human Reproduction (CEHRH) agreed with this assessment, based on data. The experiments chose doses that fall well within the range of concentrations that have been measured in mother's bloodstreams. Hence they are highly appropriate for considering risk to humans.

Question 10. Have we seen many human studies on these chemicals? Is it even possible or ethical to conduct human studies?

Answer. There have been almost no published studies of the effects of BPA on humans. There is a small number of epidemiological studies of effects of phthalates on people. They consistently report adverse effects. Endpoints range from reproductive tract malformations to sperm abnormalities to immune system problems (asthma).

None of these studies involve application of phthalates or BPA to humans. That would be unethical. They are all epidemiological studies, which examine how different levels of exposure alter the risk of specific endpoints.

Question 11. Usually chemicals are tested one at a time. However, we come into contact with numerous chemicals every day. Do these studies simulate real world exposures and what is the best way to test chemicals?

Answer. Studies that test chemicals only one at a time are insufficient to assess risks in the real world. We come into contact with hundreds, if not thousands, of chemicals every day. Sophisticated research that has been conducted over the past years shows with scientific certainty that regulations based on tests done on chemicals one-at-a-time can dramatically underestimate risks. What this research shows repeatedly is that when you have a mixture of chemicals, each one at a level that causes no effect, collectively they can cause severe damage.

Sometimes the effects are what you would expect based on the mechanisms of toxicity of the components of a mixture. But some results indicate that mixtures can cause completely unpredictable effects, for example, inducing such stress that the immune system is compromised and the animal becomes vulnerable to a common bacteria and dies from bacterial meningitis. No test in use today to develop toxicological standards takes these possibilities into account.

Testing of chemicals must start with an explicit requirement to test over a wide dose range. Current testing is usually carried out over a narrow and, compared to human exposure, relatively high level. The results of these high dose tests are then used to estimate a safe level of exposure, by incorporating safety factors that take a 'no observed adverse effect level' (NOAEL) to a 'reference' or acceptable dose, which might be 100 to 1,000 times lower than the NOAEL. That reference dose is *never* tested directly. It is assumed to be safe because of the assumption of toxicology that (above) "biological effects increase as the dose increases." But hormonally-active compounds like BPA and phthalates can have effects at low doses that are completely unpredictable from effects at high doses.

Having a complete dose-response curve is the first step in working with mixtures. Scientists have learned that under some circumstances they can combine the dose-response curves of components of a mixture to predict with reasonable accuracy how the mixture will behave. This includes examples like those described above where the levels of any one of the components was too low to cause an effect, but the effect of the mixture was very significant.

Another vital element of testing is to remove it from pressure from economic interests. Experience has repeatedly shown, with chemicals like tobacco, pharmaceuticals, lead, vinyl chloride, chromium, bisphenol A, tris, etc. that data from laboratories with economic ties to the manufacturers of the material produce data that cannot be trusted.

Another weak part of the system that leads from testing to regulatory standards is how regulatory agencies assess existing data. The overwhelming pattern is for agency assessments to give inordinate weight to industry data, even though industry data have clear biases. They often reject NIH-funded data, thus ignoring the

most sophisticated research available. This has been the overwhelming experience with bisphenol A. A parallel example with another chemical was just revealed through investigative reporting by the *Journal Sentinel* (Milwaukee, WI), in an outstanding article published on 13 July 2008. The *Journal Sentinel* published a similar analysis of bisphenol A in 2007. Here are links to the two articles.

Hazardous flame retardant found in household objects. A flame retardant that was taken out of children's pajamas more than 30 years ago after it was found to cause cancer is being used with increasing regularity in furniture, paint and even baby carriers, and EPA's safety assessment is biased toward industry, again. Milwaukee *Journal Sentinel,* Wisconsin. 13 July 2008 *http://www.jsonline.com/story/index.aspx?id=771917*.

Warning: Known to cause severe health risks to laboratory animals, bisphenol A is in you. Investigative reporting finds that the Federal Government's assurances that bisphenol A is a safe chemical are based on outdated and incomplete government studies and science mostly funded by the chemical industry. Milwaukee *Journal Sentinel,* Wisconsin. 2 December 2007 *http://www.jsonline.com/story/index.aspx?id=692145*

Question 12. What about workers who are in the plants that manufacture phthalates and BPA. Are protections in place to make sure that they aren't unnecessarily exposed?

Answer. This is a matter of significant concern because permissible occupational exposures are based upon existing standards. They will not have factored in any of the considerations that are driving concerns about endocrine disrupting compounds. Few occupational studies are available on risks of phthalates, and none for bisphenol A.

RESPONSE TO WRITTEN QUESTIONS SUBMITTED BY HON. JOHN F. KERRY TO JOHN PETERSON MYERS, PH.D.

Question 1. Why are there such dramatically different results on the low-dose effects of BPA between the results of studies sponsored by the chemical industry and studies conducted by academics or government entities?

Answer. Studies conducted by academics or government entities like the NIH use highly sophisticated methods that are at the cutting edge of medical science today. Industry funded studies, in contrast, still rely upon methods developed in the middle of the last century and use assays that are far weaker than those used by NIH-funded scientists. For example, the 'debate' over prostate effects of BPA contrasts studies by NIH-funded scientists that began with simple measurements of prostate weight (in 1997) but now involve highly sophisticated computer-based reconstructions of prostate morphology during development and analyses of changes in the ways that genes are expressed in specific key tissues of the prostate, with those of industry-funded scientists who in 2008 published yet another failed study on prostate size. Industry research has offered no conflict with the more sophisticated research because they haven't conducted it. Yet the NIH-funded work not only shows the simple weight effect but also shows how it happens in exquisite microscopic detail and reveals the molecular mechanisms that cause it to happen.

Industry funded studies also continue to be based on the assumption that "biological effects increase as the dose increases." Decades of work in basic medical science with hormones shows that to be a false assumption for chemicals that behave like hormones. BPA is a synthetic hormone.

An important historical point: The field of endocrine disruption, and specifically research on bisphenol A, has attracted many scientists from other fields who have brought into this research area tools and knowledge that have been foreign to classic toxicology. Scientists like Dr. Gail Prins (University of Illinois), Dr. Shuk Mei Ho (University of Cincinnati), Dr. Patricia Hunt (Washington State University), Dr. Anna Soto (Tufts University) and Dr. Frederick vom Saal (University of Washington) are all major players in their own fields of science, publishing in the leading scientific journals of the world and highly competitive for NIH grants. They ask questions toxicologists wouldn't have asked because they know that hormones and hormone like substances don't follow classic toxicological patterns. They bring in vastly more powerful techniques, newer and more sensitive assays, etc. They do research that is not within the ability of traditional toxicologists.

Question 2. In light of dozens of advanced studies over the past several years, in conjunction with the recent assessment from the National Toxicology Program, do you believe that the Federal Government should control exposure to BPA and phthalates?

Answer. Current science justifies regulatory action to reduce exposures to phthalates and bisphenol A. It is impossible for individual consumers to have sufficient information to make informed choices—especially when most of the time the content of consumer products is not revealed. But it should not fall to mothers to become chemical engineers and toxicological experts to buy toys and bottles for their children. For both phthalates and BPA, enough data are in hand to justify reducing exposure levels, first by eliminating their use in materials designed to hold food or water, or to purposefully come in contact with infants or babies mouths. Simultaneously, a rigorous investigation should be launched to identify other major sources of human exposure. While we know that levels in people today are higher than those sufficient to cause harm in laboratory animals, we do not have a comprehensive picture of the sources of human exposure, nor can we explain why human levels are as high as they are. Scientists suspect there are significant unidentified sources yet to be found.

Question 3. Can consumers trust products that are currently labeled as "BPA-free" or "phthalate-free"?

Answer. That is an empirical question that remains to be answered for most instances. Glass baby bottles and stainless steel sports bottles do not contain BPA. It is possible to make the products that have been labeled "BPA-free" with BPA, and "phthalate-free" without phthalates, but whether individual companies are misrepresenting their products can only be determined through analysis.

Question 4. What has been the experience of the European Union in phasing out phthalates in toys and childcare products? Has this been a significant logistical and manufacturing challenge for regulators and industry?

Answer. I don't know the answer to that question. I do know that when I visited Japan in November 2008 during the Christmas shopping season, shelves were full of plastic toys that did not contain phthalates.

Question 5. Why are low-dose effects of endocrine-disrupting chemicals like BPA and phthalates more dangerous than those of other compounds?

Answer. This question strike to the heart of a huge blind spot in the current system of establishing health standards for exposures to chemicals.

For many chemicals . . . perhaps even most, although scientists haven't asked . . . it is safe to assume that "biological effects increase as the dose increases." This assumption is at the core of how risks of exposure are assessed. The problem is that endocrinologists . . . scientists and physicians who study hormones . . . know that the effects of a hormone at one dose can be completely different, and indeed unpredictable, from the effects at another dose. High doses can be overtly toxic. Intermediate doses will turn on one set of genes but not another. Low doses will turn on yet another set of genes. The responses to those doses will be very different. If the genes turned on by low doses cause deleterious effects, as they definitely do with bisphenol A, then traditional toxicology testing will be completely blind to the risk.

I am including here an essay I wrote about this phenomenon with Dr. Frederick vom Saal. It was published in the December issue of *San Francisco Medicine,* the journal of the San Francisco Medical Society.

http://www.sfms.org/AM/Template.cfm?Section=Home&TEMPLATE=/CM/HTMLDisplay.cfm&CONTENTID=2506&SECTION=Article__Archives.

BRINGING ENVIRONMENTAL REGULATIONS UP TO DATE: SHOULD PUBLIC HEALTH STANDARDS FOR ENDOCRINE-DISRUPTING COMPOUNDS BE BASED UPON 16TH CENTURY DOGMA OR MODERN ENDOCRINOLOGY?

J.P. Myers[1] and F.S. vom Saal[2]

Health standards established in the United States for exposure to toxic chemicals rest upon a core assumption: high-dose testing procedures used in regulatory toxicology adequately predict potential low-dose effects. Scientific discoveries over the past decade have profoundly challenged that assumption as information has grown about the commonness of contaminants that behave like hormones.

Endocrinologists long ago discovered that hormones have effects at low serum concentrations that can differ dramatically, and unpredictably, from those caused at high levels.[1] Indeed, sometimes they can be diametrically opposed. This endocrinological reality stands in direct conflict with any assumption that high dose studies predict low dose impacts. If contaminants with hormonal characteristics, known as endocrine disruptors, behave similarly, then the regulatory tests used to establish safety standards may be blind to important impacts.

A growing body of research now confirms that endocrine disruptors, like hormones, can also contradict the expectations of traditional regulatory testing. This

creates the strong likelihood that some health standards currently used to set exposure limits for the American public are too weak.

To the non-endocrinologist, it seems logical that higher doses would lead to larger effects. This assumption has been at the core of toxicology for centuries, beginning with Paracelsus's 16th century observation that "All things are poison and nothing is without poison, only the dose permits something not to be poisonous." His quote has been paraphrased to "the dose makes the poison" and is generally interpreted to mean that the higher the exposure, the greater the impact.

For many contaminants, toxins, poisons and pharmaceuticals, this assumption has helped protect public health. But substantial evidence is now in hand showing that people are exposed to hundreds of chemicals, if not more, that can behave like hormones.

Some endocrine-disrupting chemicals are produced in very high volumes. The compounds of greatest concern include plastic monomers and plasticizers used widely in common consumer goods, leading to virtual ubiquitous exposure in the U.S. and other developed countries. For example, the plastic monomer, bisphenol A (BPA) was discovered to be an estrogen in the 1930s, but now it is used as the basic chemical building block for polycarbonate plastic and an epoxy resin used to line most food cans sold in U.S. supermarkets today.

The chemical characteristics of polycarbonate and the epoxy resin guarantee that normal use will contaminate food and water that comes into contact with BPA-based materials, especially if heated. Most plastic baby bottles are made with polycarbonate and baby formula cans are lined with the resin. This will result in substantial, unavoidable exposures for infants fed warmed formula.

Many studies have now shown that BPA is capable of causing a wide range of adverse effects in laboratory studies at serum concentrations beneath the median level found in people throughout the developed world.[2] The adverse effects caused by fetal exposure and infant exposure to BPA in animal experiments include breast cancer, prostate cancer, impaired fertility, cystic ovaries, uterine fibroids, hyperactivity and obesity. The current EPA and FDA health standards for BPA, however, are based upon traditional toxicological testing conducted in the 1980s. Modernizing the BPA standard based on current science would require lowering acceptable exposures by a factor of at least 5,000-fold and would require elimination of BPA from many common products.

Driven by a need to be cost-effective, regulatory toxicology has applied the 'dose makes the poison' concept in practice by testing first at high doses and then testing at successively lower doses until no response, or little response, is seen. Often only 3 or 4 doses are used and for the vast majority of chemicals these rarely if ever are low enough to be comparable to levels experienced by the general public. The assumption is that this high dose testing protocol predicts the types of effects that might take place at much lower levels. And because 'the dose makes the poison,' the expectation is that by working down the dose-response curve, from a level that clearly causes an effect to one that doesn't, this process can identify exposures beneath which there will be no harm.

Endocrinology, however, is replete with cases in which hormone action at low levels differs dramatically from hormone action at high levels. For example, administering newborn mice a high dose (1000 μg/kg/day) of the estrogenic drug diethylstilbestrol (DES) cause weight loss in adult mice. In contrast, a dose of 1 μg/kg/day causes grotesque obesity in adulthood.[3]

Another example with clinical implications comes from the well-known 'tamoxifen flare.' Tamoxifen is useful clinically because at high doses (administered daily at 20 to 40 mg daily) it is an anti-estrogen, suppressing proliferation of breast cancer cells and producing tumor regression.[4] Early during treatment, however, when tissue levels are still rising, tamoxifen administration can cause several estrogenic effects including a slight increase in tumor size. Research by Wade Welshons at the University of Missouri has explored the molecular mechanisms of the tamoxifen flare and finds that at serum concentrations 10,000 times beneath the level used to suppress breast cancer cell proliferation, tamoxifen acts as an estrogen, actually promoting proliferation.[5] Ironically, his calculations show that if one were to use standard risk assessment procedures with the tamoxifen dose-response curve—identifying the highest exposure with no discernable effect and then applying a series of safety factors that take into account various sources of uncertainty—the concentration with maximum proliferative effect would be identified as a safe level of exposure. (Welshons, pers. comm.).

In the tamoxifen flare, the dose-response curve showed inhibition at high levels and proliferation at low, *i.e.,* completely opposite effects. This is a special case of what are called non-monotonic dose-response curves: dose-response relationships in

which the slope of the line plotting response as a function of dose changes its sign (positive to negative or the reverse) somewhere over the range of doses used.

Clinicians who treat women and men for hormone-stimulated diseases (uterine fibroids, prostate cancer) advise their patients who take a hormone (Lupron) that some adverse effects occur during the initial phase of treatment. This is due to the fact that as the amount of the drug increases after injection, the low doses of Lupron result in the ovaries producing estrogen or testes to producing testosterone, and only after reaching a high dose is the drug's desired effect, inhibition of estrogen or testosterone production, achieved—opposite effects occur at low and high doses. This is not just true for hormonally active drugs, but is true for all hormones and hormone-mimicking chemicals used in products.

As research has progressed in the toxicology of endocrine-disrupting compounds, non-monotonic curves have been reported regularly.[6] One of the earliest examples involved the response of the mouse prostate to exposure to several different estrogenic compounds during fetal development.[7] These experiments examined the adult prostate weight following fetal exposure, separately, to estradiol or diethylstilbestrol (DES), and analogous non-monotonic findings now exist for BPA in human prostate cancer cells.[8] Each experimental series, conducted over an extremely wide range of doses, showed that the highest exposures did not differ from the controls, but that intermediate doses led to significant increases in prostate weight and also to sensitivity to androgen stimulation. The dose-response curve took the shape of an inverted 'U' (a descriptor now used in the literature to describe this type of non-monotonic dose-response curve). If the dose range had been extended even higher, the response would have fallen significantly beneath the controls as exposure moved into a concentration at which the compounds were overtly toxic. This was demonstrated at the level of individual genes involved in regulating prostate growth.[9]

Other endocrine-disrupting compounds demonstrating non-monotonic patterns include the phthalate DEHP, the pesticides DDE, dieldrin, endosulfan and hexachlorobenzene, and arochlor 1242, a PCB (reviewed in Myers and Hessler 2007). Some of the reported effects include strong exacerbation of allergic reactions following exposures well beneath current safety standards.

Extensive evidence is now available on the molecular and physiological mechanisms that are responsible for these findings. At very low doses hormones can stimulate the receptors in cells that allow the hormone to cause effects in the cells (called "receptor up regulation"), while at higher doses, receptor "down regulation" occurs and the number of receptors available to mediate the action of the hormone is reduced (Medlock *et al.,* 1991). Also, there are myriad hormonal feedback mechanisms between the brain, pituitary gland and hormone producing organs (thyroid gland, adrenal glands, ovaries, testes) that contribute to the presence of non-monotonic dose-response curves.

The chemical risk assessment establishment has been unresponsive to the fact that one of their core assumptions has been invalidated. Hence, no standard for any contaminant has incorporated these well-established findings from endocrinology. Instead, standards continue to be based upon testing procedures that assume high dose testing can adequately predict low dose results.

The American public depends upon regulatory agencies to set public health standards that will avoid harmful exposures. It is time that the FDA and EPA move beyond 16th Century dogma and begin using 21st Century scientific knowledge to accurately determine the safety of the chemicals being used in plastic, toys, food containers, pesticides, cosmetics, building materials, clothes—in other words, countless products and materials we incorrectly assume are safe. Given the wide range of health effects now shown to be caused in animals by exposure to these contaminants, modernizing the standards may reap large benefits for public health.

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RESPONSE TO WRITTEN QUESTION SUBMITTED BY HON. DANIEL K. INOUYE TO ELIZABETH HITCHCOCK

Question. Is there any evidence that humans can be exposed to these chemicals through the food, specifically seafood, which we eat?

Answer. In October and November 2007, Environmental Working Group surveyed the 5 leading makers of baby formula sold in the U.S. to determine whether they use BPA in their packaging. We found:

- The makers of *Nestlé, Similac, Enfamil* and *PBM* (who make store-brand formulas sold at Wal-Mart, Target, Kroger and dozens of other retailers) all said that they use BPA in the linings of metal cans holding liquid formula.
- BPA is widely used in powdered formula containers as well. Every manufacturer except Nestlé said it uses a BPA-based lining on the metal portions of their powdered formula cans. Nestlé failed to provide EWG with reliable documentation of their alternative packaging, and thus is not a clear improvement over other types.
- Powdered formulas are a better choice. Our calculations indicate that babies fed reconstituted powdered formula likely receive 8 to 20 times less BPA than those fed liquid formula from a metal can.

Liquid formula is of greatest concern, and its use could lead to high BPA exposures for babies. Recent studies documenting that BPA leaches out of plastic baby bottles prompted a run on glass bottles by concerned parents. But testing by EWG and by the Food and Drug Administration (FDA) indicates that under normal use, liquid formula itself could expose an infant to substantially more BPA than a plastic bottle. An August 2007 investigation by EWG estimated that at BPA levels found in ready-to-eat liquid formula, 1 of every 16 infants fed the formula would be exposed to the chemical at doses exceeding those that caused harm in laboratory studies.[1]

RESPONSE TO WRITTEN QUESTIONS SUBMITTED BY HON. MARK PRYOR TO ELIZABETH HITCHCOCK

Question 1. In 1998, the U.S. PIRG along with other consumer groups petitioned CPSC to ban polyvinyl chloride (PVC). In 2003, following a review by a Chronic Hazard Advisory Panel, CPSC commissioners voted to deny the petition. However, after the ruling some manufacturers have moved toward voluntarily removing phthalates from children's products. What recommendations does U.S. PIRG have for parents that are concerned about phthalates?

Answer. A few small, easy changes in the products that consumers buy and use can help reduce our children's exposure to toxic chemicals.

At the Store

Choose safer toys and teethers

Look for "PVC-free" on the labels of soft plastic toys and teethers. Another class of chemicals shown to disrupt the hormone system—phthalates—is found in polyvinyl chloride (PVC) plastic. PVC plastic is used to make different types of children's products, including some teethers and soft plastic toys. Some manufacturers have removed PVC from their children's products, especially products intended to be put

[1] Environmental Working Group, *EWG's Guide to Infant Formula and Baby Bottles,* December 2007.

into children's mouths. Unfortunately, no law requires or regulates these labels, and few products are labeled as such. When parents have a question about the chemicals in a product, they should call the manufacturer.

Choose wooden toys

There are countless manufacturers of high quality wooden toys in the market. Everything from baby rattles to kitchen play-sets are now made out of wood. Some commonly available brands include Plan Toys, Haba, Turner Toys, Selecta, and Holztiger.

Choose Safer Food Packaging and Serving Containers

- Avoid polycarbonate plastic in food containers. Check the bottom/underside of the product. If you see "PC" (usually in or near the recycling triangle) signifying polycarbonate plastic, do not purchase it. Often a number "7" on the bottom in the recycling triangle, by itself, also means the material is polycarbonate, but not always. To be safe, avoid #7 plastic. Choose plastics labeled #1, #2, or #5 in the recycling triangle, but do not heat beverages or food in plastic containers of any kind.
- Avoid PVC plastic in food containers. Check the bottom/underside of the product. If you find the number "3" in the recycling triangle, it is made from PVC plastic and should be avoided. Choose plastics labeled #1, #2, or #5 in the recycling triangle, but do not heat beverages or food in plastic containers of any kind.
- Avoid canned foods: Unfortunately, bisphenol A can leach from metal can lining into the foods and liquids contained within. Buy baby food in glass containers, and avoid feeding your child food from cans as much as possible. You can often find popular children's foods, such as tomato sauce, applesauce, and black beans, in glass jars.
- Choose safer containers for sippy cups and water bottles. Look for plastics labeled #1, #2, or #5 in the recycling triangle. As an alternative to hard plastic water bottles (such as the polycarbonate Nalgene bottles), try a lightweight stainless steel bottle instead.
- Choose glass or safer-plastic baby bottles. Almost all plastic baby bottles are made from polycarbonate plastic containing bisphenol A, but they are rarely labeled as such. With as few as 50–100 washings—even before you see wear—significant amounts of bisphenol A can leach into your baby's milk. For the best protection, switch to using glass bottles for all or most of baby's use. Contrary to claims by the plastics industry, glass bottles are extremely durable and safe (and wash well in the dishwasher). And after all, they were good enough for you when you were a baby! Evenflo is one of the only glass bottle makers around (some Babies "R" Us stores carry them and they are available on-line). A couple of manufacturers make their baby bottles from a safer polypropylene-based plastic (a softer, opaque plastic), which has not been associated with the developmental problems linked to bisphenol A.
- Choose metal feeding utensils and enamel or ceramic plates. While many manufacturers have removed phthalates from products intended to be put into young children's mouths, without a law prohibiting their use, there is no guarantee that these products, such as soft, plastic-coated feeding spoons, are made without phthalates. Look for PVC-free labels or buy stainless steel, enamel, ceramic, or glass. (Note that enamel cannot be put in the microwave, and you should not use old pottery that could have lead-based glazes).
- Avoid foods wrapped in plastic. Almost all commercial grade plastic cling wrap contains PVC plasticized with phthalates, and other plastic food packaging may be made of PVC, as well. Avoid buying foods wrapped in plastic, especially cheeses and meats. Buy deli-sliced cheeses and meats and have them wrapped in paper. If you can't avoid buying plastic-wrapped foods, cutoff a thin layer of the cheese or meat when you get home and store the remainder in glass or less-toxic plastic.

At Home

- Use glass to heat food or liquid in the microwave. You should not heat food in plastic containers or on plastic dishware, or heat liquids in plastic baby bottles. Heating food and liquids in plastic containers can cause chemicals and additives in the plastics to leach out more readily—right into baby's food and milk. While some plastic containers are marketed as "microwave safe," it is safest to avoid them for heating.

- If you do use plastic bottles, containers, or dishware, avoid harsh detergents or hot water when washing them to reduce exposure. Do not put plastic bottles, containers, or dishware in the dishwasher. Also, throw out any plastic bottles, containers, and dishware that start to look scratched or hazy. Do not let milk sit for long periods of time in plastic.
- Avoid letting your child put plastic toys in his/her mouth. Toys designed for older children are more likely to contain phthalates or bisphenol A. It is assumed that young children will not mouth these toys—such as action figures and Barbie dolls. To be safe, keep all plastic toys out of children's mouths. Call the manufacturer if you want to know if a product contains phthalates or bisphenol A.

Question 2. Since some manufacturers have taken steps to remove phthalates from certain children's products, has U.S. PIRG seen significant evidence that "phthalate-free" toys are better for children than those containing phthalates?

Answer. Some manufacturers have removed PVC from their children's products, especially products intended to be put into children's mouths. Unfortunately, no law requires or regulates these labels, and few products are labeled as such. When parents have a question about the chemicals in a product, they should call the manufacturer.

The U.S. Government, however, does not regulate the "phthalate-free" label or ensure that products labeled "phthalate-free" actually do not contain phthalates. Since the U.S. Government has not established any guidelines for what the label means, or established any standards for the phthalate content in children's products, consumers can only assume that it means phthalates are not present in the item.

In 2005, to test the reliability of the "phthalate-free" label, U.S. PIRG commissioned STAT Analysis Corporation in Chicago, Illinois to test eight soft plastic toys labeled as not containing phthalates. Of the eight toys tested, six contained detectable levels of phthalates.[2] Based on these results, we asked the Federal Trade Commission (FTC) to investigate whether manufacturers' use of the "phthalate-free" label constitutes unfair or deceptive marketing practices when the product actually contains phthalates.[3]

With the results of the FTC investigation still pending, we once again commissioned STAT Analysis Corporation in the fall of 2006 to test 10 soft plastic toys labeled as not containing phthalates.[4] Of the 10 toys tested, just two contained detectable levels of phthalates. Some of the items that tested positive for phthalates in the first year did not in the second. While this may be good news for consumers, nothing in U.S. law has changed to hold manufacturers accountable to their "phthalate-free" label or require them to stop using phthalates. Consumers still have no guarantee that the "phthalate-free" products they purchase truly are phthalate-free, as evidenced by our test results.

Question 3. Please explain the significance of low-dose exposures to BPA and how it relates to the traditionally held belief of "the dose makes the poison"?

Answer. Hundreds of studies that explore the effects of low-dose exposure to bisphenol A, pesticides and similar toxins have led to a shift in the way that many scientists and activists view toxicity. The older paradigm focused on acute toxicity, or "the dose makes the poison." This theory assumes that higher doses of a toxin will have a greater effect on the subject. The newer paradigm recognizes that exposure to even very low doses of endocrine disruptors can alter development and initiate signaling pathways, rendering the levels of toxicity that have been considered "acceptable" inaccurate. So, while exposure to bisphenol A in one given instance might be low, there is reason to believe it can still be very dangerous, and that the near constant rate of low-dose exposure is cause for alarm.

Some animal studies show adverse health affects from exposure of only 0.025 micrograms per kilogram of body weight, yet a polycarbonate baby bottle with room temperature water can leach 2 micrograms of BPA per liter. A 3-month-old baby drinking from a polycarbonate bottle may be exposed to as much as 11 micrograms per kilogram of body weight daily. The current U.S. Environmental Protection Agency daily upper limit for BPA, 50 micrograms per kilogram of body weight, is based on industry-sponsored experiments conducted in the 1980s.

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[2] U.S. PIRG Education Fund, *Trouble in Toyland: The 20th Annual Survey of Toy Safety,* November 2005.

[3] Letter to The Honorable Deborah Platt Majoras, Chairman, FTC, November 21, 2005. On file with the author. Our petition was later denied.

[4] Eight of the toys were labeled "phthalate-free" on the packaging. One item was labeled "phthalate-free" on the manufacturer's website. For the last item, the manufacturer's website claimed not to use phthalates in any of its children's products.

BPA raises particularly troubling health questions because it can affect the endocrine system, mimicking the effects of estrogen in the body. Experiments in animals and with human cells strongly suggest exposures typical in the U.S. population may increase susceptibility to breast and prostate cancer, reproductive system abnormalities, and, for exposure in the womb and early childhood, a host of developmental problems. Concerns about early life exposures also extend to early onset of puberty in females, potential prostate problems in males, and obesity.

Question 4. How is the average person exposed to phthalates?

Answer. Phthalates are used to build cars, homes and offices. They are used in cosmetics, toys and medical devices, and they are used to package food.[5] Because of their widespread use, Americans are constantly exposed to these chemicals. Phthalates leach out of the plastics that contain them making the chemicals available for inhalation, ingestion and absorption.[6] Because of this, we are exposed to phthalates when we touch the products that contain them. We are also exposed to phthalates because they come out of their original sources and into the air that we breathe.[7]

Question 5. What is the best way to reduce exposure to phthalates?

Answer. The best way to reduce exposure to phthalates is to phaseout their use. Both Federal and state governments should act to regulate these chemicals, especially in children's products. Congress should require that chemical manufacturers demonstrate the safety of their products before putting them on the market. The Consumer Product Safety Commission should protect consumers from these hazardous products. First, the Commission should take a precautionary approach to the chemicals in products. Second, the Commission should require products to be labeled appropriately.

Question 6. Please explain the significance of phthalate mixtures.

Answer. When used in combination with other phthalates, there is an additive dose-response relationship. A study by scientists at the EPA and the North Carolina State University showed that phthalates with similar action mechanisms have a dose additive effect on fetal testosterone when administered in combination.[8] Another study by scientists at the University of Surrey in the United Kingdom showed that a mixture of phthalates caused a seemingly additive effect of serum cholesterol in rats.[9]

Question 7. What are endocrine disruptors and how do they affect us?

Answer. Endocrine disruptors are chemicals that mimic or block hormones or interfere with hormone production.[10] Hormones transfer signals between cells over long distances using the bloodstream. Once a hormone reaches a cell, it fits into a receptor and initiates a cell response using the signal transduction pathway. If a different molecule is substituted for the hormone in the receptor, then the cell will receive alternate instructions.[11] Hormone blockers prevent hormones from delivering signals from one cell to another. Hormone replacers replace hormones and send either excessive or insufficient signals to cells. The change in the signals received by cells alters the cells response and thus how the body functions. Because of these actions, endocrine disruptors impede normal functions and cause damage to the body. Endocrine disruptors have been linked with abnormalities in the repro-

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[10] The Natural Institute of Environmental Health Sciences. "Endocrine disruptors" Downloaded on June 19, 2008 at *http://www.niehs.nih.gov/health/topics/agents/endocrine/docs/endocrine-disruptors.pdf*.

[11] Sadava, David, H. Craig Heller, Gordon H. Orians, William K. Purves, David M. Hillis *Life: The Science of Biology 8th edition* Sinauer Associates, Inc. 2007.

ductive, immune, nervous and endocrine systems.[12] Endocrine disruptors can cause decreased sperm count and testicular cancer. They can also interfere with proper immune function causing immunotoxicity. They can effect the nervous system by limiting thyroid function and thus brain development. They can also cause endometriosis, which leads to infertility in women.

Question 8. Is there an established list of known endocrine disruptors?

Answer. In 2007 the Environmental Protection Agency (EPA) compiled a draft list of endocrine disruptors that was selected on the basis of exposure potential. The EPA is now investigating these chemicals and is planning to issue a final list.[13] Although there is no governmental list of known endocrine disruptors, scientists have identified many chemicals as such. Paul Geottlich has a list of known endocrine disruptors published in *Fundamentals of Naturopathic Endocrinology.*[14]

Question 9. Are there already alternatives to BPA and phthalates? Are these alternatives safer than what is currently being used? What science or studies exists into these alternatives?

Answer. Several products that are made with phthalates or BPA could easily be made with alternatives. Phthalates can be replaced with either polymeric or adipate plasticizers.[15] A study at Cochin University of Science and Technology showed the use of polymeric plasticizers reduces the leaching of chemicals from PVC.[16] A study performed by the Institute of Food Safety and Nutrition in conjunction with the Danish Veterinary and Food Administration found that adipate plasticizers did not induce the antiandrogenic effects that phthalates induce.[17] Another alternative to using phthalates is to switch from PVC to other plastics such as thermoplastic elastomers, ethylene vinyl acetate and polyolefins.[18] The alternatives are also safer than PVC. The alternatives to PVC plastic are only 2 percent plasticizers, while the phthalate content in PVC is up to 50 percent. Furthermore the alternatives are less likely to leach plasticizers when compared to PVC.[19] Both alternatives pose little safety concern and offer flexibility in the production process. Products made with polycarbonate plastic containing BPA could instead be made with polyamide, a plastic that does not require BPA for production.[20] The alternatives to BPA have not been as heavily tested as the alternatives to phthalates. Polyamide plastic is not known to contain harmful plasticizers, and so the effects of polyamide on human health is believed to be negligible.[21]

Question 10. Do infants and children have the same immune and endocrine system as adults? Do studies take into account these differences?

Answer. People are born with all of the necessary organs in the immune and endocrine system; however these organs are not developed. They will grow and develop during infancy and childhood. Because infants and children have immune and endocrine systems that are developing, they are more susceptible to interaction with and damage from dangerous chemicals. Several studies are designed to account for this, as well as for the developmental effects of phthalates and BPA on the human systems. A study conducted at the Mitsubishi Chemical Safety Institute exposed female rats to phthalates during gestation.[22] The study found that exposure to phthalates during development caused inhibition in weight gain of offspring as well as abnor-

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[12] World Health Organization. "Global Assessment of the state-of-the-science of endocrine disruptors" WH/PCS/EDC/02.2 (2002)

[13] *www.epa.gov/endo.*

[14] Michael, Dr. Friedman. (ed.) *Fundamentals of Naturopathic Endocrinology*. CCNM Press (2005)

[15] Svoboda, Ronald D. "Polymeric Plasticizers for Higher Performance Flexible PVC" The C.P. Hall Company. Chicago, IL.

[16] Sunny, M.C., P. Ramesh and K.E. George. "Use of polymeric Plasticizers in Polyvinyl Chloride to Reduce Conventional Plasticizer Migration for Critical Applications" *Journal of Elastomers and Plastics* 36:1:19–31 (2004).

[17] Dalgaard M. *et al.* "Di(2-ethylhexyl) adipate (DEHA) induced developmental toxicity but not antiandrogenic effects in pre- and post-natally exposed Wistar rats" *Reproductive Toxicology*. March–April 2003 17(2):163–170.

[18] Tickner, Joel. "Review of the Availability of Plastic Substitutes for Soft PVC in Toys" Department of Work Environment. University of Massachusetts at Lowell, USA.

[19] Tickner, Joel. "Review of the Availability of Plastic Substitutes for Soft PVC.

[20] McNichols, Jeremiah "Sippy Cup Showdown: Safer BPA-Free Drinkware for Toddlers" accessed July 19, 2008 at *http://zrecs.blogspot.com/2007/05/sippy-cup-showdown-safer-bpa-free-sippy.html.*

[21] Labour Environmental Alliance Society "Frequently Asked Questions" accessed Jun. 23, 2008 at *www.leas.ca/Frequently-Asked-Questions.htm.*

[22] Hoshino N. *et al.,* "A two-generation reproductive toxicity study of dicyclohexyl phthalate in rats." *Journal of Toxicological Science.* Dec. 2005 30 Spec No. 79–96.

mal reproductive development among male and female rats in the first and second generations.

Question 11. Have we seen many human studies on these chemicals? Is it even possible or ethical to conduct human studies?

Answer. Epidemiologic studies are often conducted in place of clinical trials, because they do not present the same ethical issues. Several epidemiologic studies have been conducted regarding phthalates, BPA and their effects on humans. Three studies, one at Fudan University's School of Public Health in Shanghai and two at the Harvard School of Public Health, showed an association between phthalate exposure and reduced semen quality in adult males.[23]

Question 12. Usually chemicals are tested one at a time. However, we come into contact with numerous chemicals every day. Do these studies simulate real world exposures and what is the best way to test chemicals?

Answer. Chemicals are tested individually or in carefully controlled groups because it eliminates possible sources of error and confounding in the study. When only a single chemical is administered, the effect on the subject can be linked strongly to the chemical. Furthermore if two chemicals are administered together, then the possibility of interaction between these chemicals must be considered, multiplying the possibilities of what causes the result.

Studies that test chemicals individually simulate individual pathways of exposure focusing on the elements of exposure that are most easily reduced. The studies have focused on the presence of phthalates and BPA in children's products for several reasons. First, phthalates and BPA pose special hazards to infants and children. Second, the elimination of phthalates and BPA in toys is more easily achieved, since toys and childcare products do not exist as long in the market as cars and carpets. Third, the exposure of children to phthalates and BPA in childcare products can be more easily controlled in an experimental setting.

Question 13. What about workers who are in the plants that manufacture phthalates and BPA. Are protections in place to make sure that they aren't unnecessarily exposed?

Answer. In addition to basic safety measures taken when chemicals are used in production, the Occupational Safety and Health Administration has established limits on the amount of certain phthalates and BPA to which workers may be exposed.[24] In air, concentrations can not exceed 0.5 mg/m^3 for DEHP, 5 mg/m^3 for DEP. Bisphenol-A should not exceed 860 mg/m^3 in air concentration.

RESPONSE TO WRITTEN QUESTIONS SUBMITTED BY HON. JOHN F. KERRY TO ELIZABETH HITCHCOCK

Question 1. Why are there such dramatically different results on the low-dose effects of BPA between the results of studies sponsored by the chemical industry and studies conducted by academics or government entities?

Answer. A recently-published review of scientific studies shows that, in the last 7 years (through November 2005), 151 studies on the low-dose effects of BPA have been published.[25] None of the 12 studies funded by the chemical industry reported adverse effects at low levels, whereas 128 of 139 government-funded studies found effects. These many studies were conducted in academic laboratories in the U.S. and abroad.

Even the 12 industry-funded studies have flaws, however. Of the industry studies, two had its positive control fail—an indication that the entire experiment had failed, not that BPA had not caused an effect. Another industry study concluded BPA caused no effect, but an independent analysis of the experiment's data by scientists convened by the National Toxicology Program of the U.S. Department of Health & Human Services concluded that in fact there was an effect. Industry scientists had misreported their own results.

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[23] Zhang Y.H. *et al.,* "Phthalates exposure and semen quality in Shanghai: a cross-sectional study" *Biomedical Environmental Science* June 2006 19(3):205–209; Duty S.M. *et al.,* "Phthalate Exposure and human semen parameters" Epidemiology. May 2003 14(3):269–277; Hauser R. *et al.,* "Altered semen quality in relation to urinary concentration of phthalate monoester and oxidative metabolites" *Epidemiology* Nov. 2006 17(6):682–691.

[24] The Occupational Safety and Hazard Administration *Regulations (Standards—29C FR)* Air Contaminants 1915.1000.

[25] vom Saal, F. and C. Hughes, An Extensive New Literature Concerning Low-Dose Effects of Bisphenol A Shows the Need for a New Risk Assessment. *Environmental Health Perspectives* 113:926–933 (2005).

The chemical industry relies on an incomplete review of scientific studies by an effort funded by the American Plastics Council at the Harvard Center for Risk Analysis. The panel funded by the American Plastics Council only considered 19 studies in concluding in 2004 that the weight of the evidence for low-dose effects of BPA was weak.[26] As of November 2005, there were 151 published studies on the low-dose effects of BPA.

Question 2. In light of dozens of advanced studies over the past several years, in conjunction with the recent assessment from the National Toxicology Program, do you believe that the Federal Government should control exposure to BPA and phthalates?

Answer. The Federal Government has an obligation to protect consumers from dangerous products. The CPSC should first label products containing Bisphenol A and phthalates with the names of the chemicals they contain to allow parents to choose less toxic products. Second, the CPSC should take the precautionary approach and require manufacturers to remove chemicals that may pose a particular threat to fetuses, infants and children, particularly when the chemical is not necessary for the product to function according to design. In addition, CPSC and the Federal Trade Commission should look into manufacturers' use of the "phthalate-free" label and take action against manufacturers that may be misleading consumers.

Congress has the opportunity to take action on these two chemicals now. The final version of CPSC reform legislation now in conference should include the Feinstein amendment banning phthalates in children's products (incorporated as Section 40 of H.R. 4040 as passed by the Senate). The amendment will:

- Prohibit the use of phthalates (any combination of certain listed chemicals in concentrations exceeding 0.1 percent) in any children's product or child care article.
- Require manufacturers to use the least toxic alternative to phthalates.
- Prohibit the use of certain harmful alternatives—including substances known to be, likely to be, or suggestive of being carcinogens; and reproductive toxicants identified as causing either birth defects, reproductive harm, or developmental harm.
- The amendment also includes an important "savings clause" that would prevent Federal preemption of stronger state laws regulating phthalates in toys or other product categories.

In addition, U.S. PIRG supports legislation introduced by Senator Schumer (NY) and Rep. Markey (MA) that would ban bisphenol A in children's products or in food containers.

Question 3. Can consumers trust products that are currently labeled as "BPA-free" or "phthalate-free"?

Answer. Some manufacturers label their baby products and toys as "phthalate-free," which should provide parents the information they need to make educated purchasing decisions. The U.S. Government, however, does not regulate the "phthalate-free" label or ensure that products labeled "phthalate-free" actually do not contain phthalates. Since the U.S. Government has not established any guidelines for what the label means, or established any standards for the phthalate content in children's products, consumers can only assume that it means phthalates are not present in the item.

In 2005, to test the reliability of the "phthalate-free" label, U.S. PIRG commissioned STAT Analysis Corporation in Chicago, Illinois to test eight soft plastic toys labeled as not containing phthalates. Of the eight toys tested, six contained detect-

[26] vom Saal, F. and C. Hughes, An Extensive New Literature Concerning Low-Dose Effects of Bisphenol A Shows the Need for a New Risk Assessment. *Environmental Health Perspectives* 113:926–933 (2005) ("The charge to the HCRA panel, which was to perform a weight-of-the evidence evaluation of available data on the developmental and reproductive effects of exposure to BPA in laboratory animals, led to an analysis of only 19 of 47 available published studies on low-dose effects of BPA. *The deliberations of the HCRA were in 2001–2002, and accordingly, a cut-off date of April 2002 was selected for consideration of the published literature.* It is regrettable that the relevance of the analysis was further undermined by a delay of 2.5 years in publication of the report. *During the intervening time, between April 2002 and the end of 2004, a large number of additional articles reporting low-dose effects of BPA in experimental animals have been published.* The result is that by the end of 2004, a PubMed (National Library of Medicine, Bethesda, MD) search identified 115 published studies concerning effects of low doses of BPA in experimental animals.").

able levels of phthalates.[27] Based on these results, we asked the Federal Trade Commission (FTC) to investigate whether manufacturers' use of the "phthalate-free" label constitutes unfair or deceptive marketing practices when the product actually contains phthalates.[28]

With the results of the FTC investigation still pending, we once again commissioned STAT Analysis Corporation in the fall of 2006 to test 10 soft plastic toys labeled as not containing phthalates.[29] Of the 10 toys tested, just two contained detectable levels of phthalates. Some of the items that tested positive for phthalates in the first year did not in the second. While this may be good news for consumers, nothing in U.S. law has changed to hold manufacturers accountable to their "phthalate-free" label or require them to stop using phthalates. Consumers still have no guarantee that the "phthalate-free" products they purchase truly are phthalate-free, as evidenced by our test results.

Question 4. Why are low-dose effects of endocrine-disrupting chemicals like BPA and phthalates more dangerous than those of other compounds?

Answer. See answer above to Senator Pryor's similar question.

RESPONSE TO WRITTEN QUESTIONS SUBMITTED BY HON. MARK PRYOR TO STEVEN G. HENTGES, PH.D.

Question 1. The "low-dose hypothesis" claims that exposure to extremely low levels of certain substances could cause adverse health effects in humans. Some have criticized existing studies and reviews for looking at only high dosage exposure. How would you respond to those that claim either lack of evidence supporting the use of these chemicals or that low dose evidence demonstrates a concerned risk?

Answer. Many hundreds of studies on bisphenol A have been conducted in the last 10 years and a substantial percentage of these studies were aimed at addressing the question whether bisphenol A could cause adverse health effects at very low doses. These studies are not all equivalent, and in general, they vary vastly in size, scope, quality and relevance to human health. The most comprehensive studies cover multiple generations of laboratory animals, are large in scale and statistically powerful, include a wide range of doses from very low to very high, and dose animals by the most relevant oral route of exposure. Other studies are small in size and scope, may be poorly conducted or reported, and dose animals by routes that are of little or no relevance to humans (*e.g.,* subcutaneous injection, direct injection into the brain). A further complication is that the results of these many studies are not consistent and often are conflicting.

When faced with a large and diverse body of data, as is the case for bisphenol A, scientists systematically evaluate the weight of scientific evidence to draw conclusions based on all of the available evidence. In recent years, numerous weight of evidence evaluations of bisphenol A have been conducted by independent scientific and government bodies worldwide. These evaluations consistently support the conclusion that bisphenol A is not a significant risk to human health, in particular at the very low levels to which people could be exposed through use of consumer products.

In addition to evaluating each available study on its own merits, a weight of evidence evaluation also assesses whether the findings of studies have been replicated or corroborated in independent laboratories, whether they are consistent within and across studies, and whether they are coherent when considered together. Repeatability is a fundamental principle of the scientific process; findings that cannot be replicated in robust studies cannot be accepted as valid.

Since much of the recent research on bisphenol A is aimed specifically at assessing the potential for bisphenol A to cause health effects at low doses, the many recent weight of evidence evaluations are focused almost entirely on this question. None of these evaluations are focused only at high dose exposures. The conclusions of these evaluations are based on the full weight of scientific evidence, including all relevant studies that report effects at low doses and studies that do not report low dose effects.

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[27] U.S. PIRG Education Fund, *Trouble in Toyland: The 20th Annual Survey of Toy Safety,* November 2005.

[28] Letter to The Honorable Deborah Platt Majoras, Chairman, FTC, November 21, 2005. On file with the author. Our petition was later denied.

[29] Eight of the toys were labeled "phthalate-free" on the packaging. One item was labeled "phthalate-free" on the manufacturer's website. For the last item, the manufacturer's website claimed not to use phthalates in any of its children's products.

Question 2. There seems to be a marked difference between studies funded by the chemical industry, those funded by governments, and those conducted by academic institutions. How have these studies differed to produce such opposite results?

Answer. We understand this question to be directed to the body of scientific literature on bisphenol A and not generally with respect to the entire chemical industry, so we answer it here.

Scientific studies can only answer questions they are designed to answer. Studies sponsored by industry are typically, but not always, aimed at answering the critical question of whether a product is safe for use. These studies are generally designed to meet the requirements of internationally accepted test guidelines that were developed for this purpose. The studies are typically large in scale to be sure the studies have adequate statistical power and examine appropriate endpoints to address the question that the study is intended to answer. The studies are also typically conducted in highly qualified test laboratories under Good Laboratory Practices, which provides further assurance of the integrity of the study results.

Other studies, which can also include industry sponsored studies, are often aimed at other scientific questions that may or may not be directly relevant to assessing human health concerns. These studies may be limited in scope and examine endpoints that are difficult to interpret with respect to the safety of the substance being tested. Some studies, although scientifically well conducted, may have limited or no relevance for assessing human health concerns.

For bisphenol A, a very wide diversity of studies have been conducted and it is a gross oversimplification to say that studies sponsored by the chemical industry have opposite results to studies conducted by academic institutions. Very often, studies cannot be directly compared because they are so different.

As described in the answer to the question above, all relevant studies on bisphenol A have been systematically assessed in numerous weight of evidence evaluations. When all of the relevant data from these many studies are compared, in particular to determine whether the findings are repeatable or corroborated in independent laboratories, the most consistent result is that no effects from exposure to low doses of bisphenol A are reliably found. This conclusion is true even if the analysis is limited to non-industry studies. In that regard, studies sponsored by industry are consistent with the broader database and validate the overall conclusion that low doses of bisphenol A have not been reliably shown to cause adverse health effects.

Question 3. Please explain the significance of low-dose exposures to bisphenol A and how it relates to the traditionally held belief of "the dose makes the poison"?

Answer. The so-called "low-dose hypothesis" asserts that very low doses of endocrine-active substances may cause adverse health effects at very low doses. In particular, such low-dose health effects are postulated to occur with a non-monotonic dose-response, which means that health effects observed at very low doses would not be observed at higher doses. This hypothesis has not been scientifically proven and there is at best limited evidence that it could be valid.

A fundamental principle of toxicology is commonly expressed as "the dose makes the poison," which means that health effects observed at a particular dose will uniformly increase in intensity or severity as the dose is increased. Conversely, as the dose is decreased, a dose causing no effect can be found (a no-effect level) and any lower dose will also cause no effect. This is referred to as a monotonic dose-response (sometimes called a linear dose-response).

Toxicology studies are often designed to identify a dose at which no adverse effects occur, which is referred to as a No-Observed-Adverse-Effect-Level (NOAEL). Doses below the NOAEL may not be tested experimentally since no adverse effects are expected. If the low-dose hypothesis is valid, health effects below the NOAEL might occur but not be found.

In response to the low-dose hypothesis, there are now a large number of studies on bisphenol A that examined low doses well below the accepted NOAEL. Most of these studies did not examine a sufficient number or range of doses to determine whether any dose-response is monotonic or non-monotonic and are thus not capable of validating the low-dose hypothesis.

It is important to note that the accepted NOAEL for bisphenol A is based on the most comprehensive studies, which were conducted over multiple generations of laboratory animals and included a wide range of doses from very low doses up to a very high dose above the NOAEL that induces toxicity. These studies do not validate claims that bisphenol A causes adverse effects at low doses, regardless of the dose-response, and only monotonic dose-responses were observed. These studies provide the most powerful evidence that the low-dose hypothesis, at least for bisphenol A, is not valid.

Beyond bisphenol A, the biological plausibility of the low-dose hypothesis is not supported by research on other endocrine-active substances. For example, two very robust and comprehensive studies have recently been published on estradiol and ethinylestradiol, the first being the prototypical naturally occurring estrogen and the second being the estrogenic substance commonly used in birth control pills. Both studies covered a wide dose range and neither study found non-monotonic dose-response for any observed effect. In comparison to these two substances, bisphenol A is a very weak estrogen that is 10,000–100,000 times less potent. No plausible explanation has been advanced to explain why bisphenol A would cause adverse effects at low doses with non-monotonic dose-response while more potent estrogens would not do so.

There is at best very limited evidence to support the validity of the low-dose hypothesis and very strong evidence that indicates the hypothesis is not valid. Lacking reliable evidence and biological plausibility, the low-dose hypothesis is just that—a hypothesis that has not been proven.

Question 4. Have or haven't we seen many human studies on bisphenol A? Is it even possible or ethical to conduct human studies?

Answer. In our general answers, we note that there are different types of studies that could involve humans, some of which are considered ethical and some of which are not. Here we address the question with specific reference to bisphenol A.

Several human studies have been conducted to understand how bisphenol A is processed in the body. In these studies, human volunteers are treated with a small dose of bisphenol A that is well below a dose that could cause toxicity as determined from reliable studies on laboratory animals. The objective of these studies is to determine whether bisphenol A is absorbed, where it is distributed in the body, whether it is metabolized and to what metabolites, and how quickly and where it is excreted.

These studies confirm that people efficiently convert bisphenol A, as it is absorbed, to a metabolite that has no known biological activity, and then quickly excrete that metabolite with a half-life of about 5 hours. This means that bisphenol A is eliminated from the body into urine within the day of exposure and does not accumulate in the body. Of equal importance is that these studies also identified a critical difference between how rodents and humans process bisphenol A. The amount of time that bisphenol A remains in the body is substantially shorter for humans compared to rodents, which indicates that people are likely to be less sensitive to any potential health effects from exposure to bisphenol A. This is significant since most laboratory animal studies on bisphenol A have been conducted on rodents (*e.g.,* mice, rats), which could overestimate human health concerns.

A second type of study on humans that has been performed with respect to bisphenol A is biomonitoring to measure the presence of trace levels of chemicals in the body. Biomonitoring data provides a direct measure of exposure, which is necessary to assess whether bisphenol A poses a risk to humans. Since bisphenol A is entirely and quickly excreted into urine in the form of a metabolite, most biomonitoring studies measure the amount of that metabolite in urine samples. The largest set of biomonitoring data on bisphenol A is from the CDC National Health and Nutrition Examination Survey (NHANES), which is an ongoing population-scale program. That data was recently published and is generally consistent with the results of many smaller scale studies conducted around the world. Collectively these studies demonstrate that human exposure to bisphenol A is extremely low, which confirms what is expected in light of the use patterns of bisphenol A. Almost all bisphenol A is chemically reacted to form plastics and resins, meaning that there are no consumer products that contain any more than trace residual levels of bisphenol A. The typical level of bisphenol A found in human urine corresponds to an exposure level that is approximately 500–1,000 times below the science-based safety standard recently established in Europe based on an up-to-date review of the science.

A small number of small-scale epidemiology studies, which attempt to associate human exposure to bisphenol A with specific health effects, have also been conducted. Biomonitoring measurements have been used in all of the available studies to quantify human exposure. The earliest such studies used an analytical method that was subsequently found to be invalid and are thus fatally flawed. More recent studies have used analytical methods that are likely to be valid, including several studies in which the measurements were conducted by CDC researchers. Although these studies have found no associations between exposure to bisphenol A and the examined health effects (*e.g.,* birth weight and related parameters, earlier age of puberty in girls, endometriosis in adult women), the studies are limited and do not provide definitive results, which would require longer term and larger scale studies.

Question 5. Are there already alternatives to BPA? Are these alternatives safer than what is currently being used? What science or studies exists into these alternatives?

Answer. Bisphenol A is primarily used to make polycarbonate plastic and epoxy resins. Since neither of these materials would exist without bisphenol A, alternatives to bisphenol A effectively means alternatives to these materials.

Both of these materials are used in a wide array of consumer and industrial products. As a general matter, they are used in these products because their key properties provide a necessary function and they are often the material of choice to provide that function. In short, they are used because they work.

Polycarbonate plastic is a lightweight, clear and highly shatter-resistant material that makes it useful in products such as sports safety equipment (*e.g.,* bicycle and football helmets), CDs and DVDs, housings on electrical and electronic equipment (*e.g.,* computers, cell phones, appliances), eyeglass lenses and components of medical devices, and automotive components, as well as baby bottles, water bottles and food storage containers.

Epoxy resins are durable and chemically resistant materials that function well as protective coatings on metal products and as laminates in electronic circuit boards. Along with coatings on structural steel and pipes and fittings, epoxy resins are widely used as the protective coating on most food and beverage cans where they protect the safety and integrity of the contents. Without a coating, foods and beverages can corrode the metal can, resulting in contamination of food with metals and potentially with harmful bacteria if the integrity of the can is breached.

To our knowledge, there are no alternatives that could easily substitute for all applications of these materials. In each case, a variety of factors must be considered to identify suitable alternatives, and the critical requirements for each application vary considerably. For any alternative, two immediate hurdles are functionality (*i.e.,* the alternative must provide the function needed for that application) and safety (*i.e.,* the alternative must be safe for the application).

Compared to bisphenol A, no alternative has been so well tested or vetted so thoroughly by government agencies. Consequently, it is not likely that scientific data exists to support a claim that any alternative is safer than bisphenol A.

Question 6. What about workers who are in the plants that manufacture BPA. Are protections in place to make sure that they aren't unnecessarily exposed?

Answer. Bisphenol A is manufactured in a closed process that offers little opportunity for human exposure. Since bisphenol A is a high melting solid with very low volatility, the primary opportunity for occupational exposure in plants that manufacture bisphenol A involves contact with dust, in particular skin contact. Studies have shown that transfer of bisphenol A through skin into the body is limited and the primary health concern is for skin irritation or sensitization. Personal protection equipment is used to limit worker exposure to bisphenol A in circumstances where there is the potential for contact with bisphenol A.

Question 7. How is the average person exposed to phthalates? What is the best way to reduce exposure to phthalates?

Answer. Exposure to phthalates comes from many sources. These are a very valuable class of chemicals; different phthalates are used in personal care products, inks, caulks, sealants and vinyl products. A review of the scientific literature suggests that the greatest exposure to phthalates is through ingestion of food. Data from the U.S. Center for Disease Control indicates that total exposures to the general U.S. population from phthalate esters from all sources are well within EPA reference doses.

Question 8. Please explain the significance of phthalate mixtures.

Answer. There are about 13 phthalates commonly used today, so there can be exposure to multiple phthalates. Data from recent U.S. Centers for Disease Control (CDC) biomonitoring data indicates that humans are exposed to extremely low levels of several phthalates simultaneously. The CDC data indicates that the general population's exposure for each phthalate measured is below its EPA reference dose. A reference dose is an exposure level defined by the Environmental Protection Agency as "a numerical estimate of a daily oral exposure to the human population, including sensitive subgroups such as children, that is not likely to cause harmful effects during a lifetime."

Some have suggested that while exposures to one phthalate ester are below the reference dose, scientists should also study whether more than one phthalate could interact. The evidence indicates that for the few chemicals that we know do interact, most do so by a process called "additivity," in which the effects of these chemicals are added together. But in order to be "additive," chemicals must produce their effects not only on the same organ systems, but in the same way. In a toxicologist's

terms, their "mechanism of action" in the body has to be the same for the effects to be additive. Another important point relates to the exposure levels. To produce meaningful interactions, exposures must be at levels at which the respective chemicals produce effects. If the exposures are below a critical threshold, an "additive" effect would not generally be expected. This is an emerging field of study.

Importantly, it is seen from the CDC data that maximum exposure in the most sensitive human subpopulations are still orders of magnitude less than doses with which additivity has been demonstrated in rodents.[1] Since the current reference dose for DBP (EPA IRIS) is 0.3 mg/kg/day, the estimated theoretical toxicity threshold for combined exposure to the phthalates DEHP, DBP, DIBP, and BBP would also be orders of magnitude higher than the EPA reference dose for DBP based on the simple dose addition model.

Question 9. Have or haven't we seen many human studies on phthalates? Is it even possible or ethical to conduct human studies?

Answer. In our general answers, we note that there different types of studies that could involve humans, some of which are considered ethical and some of which are not.

Several human studies have been conducted to understand how phthalate esters are processed in the body. In these studies, human volunteers are treated with a small dose of phthalate esters that are well below a dose that could cause toxicity as determined from reliable studies on laboratory animals. The objective of these studies is to determine whether phthalate esters are absorbed, where they are distributed in the body, whether they are metabolized and to what metabolites, and how quickly and where they are excreted.

These studies confirm that people efficiently convert phthalate esters to metabolites, which are then quickly excreted through urine in about twenty-four hours of exposure and not accumulated in the body.

A second type of study on humans that has been performed with respect to phthalate esters is biomonitoring to measure the presence of trace levels of chemicals in the body. Biomonitoring data provides a direct measure of exposure, and understanding exposure is necessary to assess whether phthalate esters pose a risk to humans. Since phthalate esters are excreted into urine in the form of metabolites, most biomonitoring studies measure the amount of the metabolites in urine samples. The largest set of biomonitoring data on phthalate esters is from the CDC National Health and Nutrition Examination Survey (NHANES), which is an ongoing population-scale program. The CDC data demonstrate that human exposure to phthalate esters is extremely low, and below EPA reference doses for those compounds.

A small number of small-scale epidemiology studies, which attempt to associate human exposure to phthalate esters with specific health effects, have also been conducted. Biomonitoring measurements have been used in all of the available studies to quantify human exposure. To date, the studies are limited and do not provide definitive results, which would require longer term and larger scale studies. EPA has declined to rely on data from these early studies due to their limitations.

Question 10. Are there already alternatives to phthalates? Are these alternatives safer than what is currently being used? What science or studies exists into these alternatives?

Answer. Phthalates have been used to make vinyl soft and flexible for many years since their chemical properties make them the most suitable softeners for a wide range of consumer and industrial products. Several non-phthalate plasticizers are commercially available; however, each one's suitability for use as a phthalate alternative depends on the technical requirements for the particular application (*i.e.,* will the finished product perform satisfactorily). By way of example, many important medical applications depend on the performance of flexible vinyl tubing. Soft tubing adds patient comfort when patients are intubated; in addition, plasticized tubing resists kinking and holds its shape, helping in the administration of the correct dosage of drugs and treatments. One can easily see that in evaluating whether there might be an alternative to phthalates in such an application, doctors could insist that any alternative perform equally as well or better in the delivery of key medical services. And one can also easily see how a hospital administrator, charged with keeping costs down, might likewise insist on cost equivalence before moving to an alternative plasticizer.

The recently published report on alternatives to DEHP in medical devices by the European Scientific Committee on Emerging and New-Identified Health Risks

[1] Maximum estimated human daily exposure to one of the most commonly used phthalates, DEHP, was calculated from measurements in children aged 3–14 (0.0031 mg/kg/d.).

(SCENIHR) provides the most up to date summary of data available on the most common alternative plasticizers. The report shows that some products have been as broadly studied as phthalates but that several have not. A few of the alternatives also have been reviewed in recent safety assessments.[2]

The most commonly used phthalates perform well, are economical, and have a rich toxicological database; more important, government safety assessments have consistently concluded that they may continue to be used safely in many applications, despite some concerns for a few applications where high exposures may be possible.

Question 11. What about workers who are in the plants that manufacture phthalates. Are protections in place to make sure that they aren't unnecessarily exposed?

Answer. Typically phthalates are manufactured in closed systems and the operator controls the reaction remotely on a computer terminal so worker exposure in manufacturing facilities is very low.

Question 12. What are endocrine disruptors and how do they affect us?

Answer. The term "endocrine disruptor" (ED) was invented in 1991 at a World Wildlife fund-sponsored conference held at the Wingspread retreat in Racine, Wisconsin (Colborn and Clement 1992). The participants cited environmental and experimental findings in fish and wildlife, *in vitro* study results, and clinical findings in humans exposed to high levels of the clinically prescribed pharmaceutical diethylstilbestrol (DES) as the basis for the ED hypothesis. Under the ED hypothesis, the most relevant question is not whether highly potent pharmaceutical agents can cause effects, but rather are the exposures to trace ambient environmental levels of substances of sufficient magnitude and duration to exert adverse effects on the general population?

Various organizations have held numerous conferences on the ED issue, and several have wrestled with the term ED. The term ED remains somewhat controversial because of the imprecise and inconsistent manner in which it is applied. Many use the term very broadly, such that many substances have been implied by some to be EDs, despite no evidence of harm. One of the clearer and most useful definitions of ED (and potential ED) was published by the "European Workshop on the Impact of Endocrine Disrupters on Human Health and Wildlife" held in Weybridge, UK (1996):

- "An endocrine disrupter is an exogenous substance that causes adverse health effects in an intact organism, or its progeny, secondary to changes in endocrine function."
- "A potential endocrine disrupter is a substance that possesses properties that might be expected to lead to endocrine disruption in an intact organism."

Scientists have agreed that the definition requires that an ED have a link between the endocrine activity and some adverse health effect; otherwise the endocrine effect is not toxicologically significant. While some groups have lobbied for a broader and less rigorous definition, scientists have, across a variety of conferences and venues, consistently agreed with a definition identical to or very similar to the Weybridge definition.

A number of excellent and comprehensive reviews of endocrine disruption studies have been published. Collectively, these reviews represent a significant body of scientific work compiled and or reviewed by more than 500 scientists across the world, resulting in extensive volumes covering human and wildlife toxicology, mechanisms of action, risk assessment, testing, test method development and validation, and other science policy concerns (NRC 1999; U.S. EPA 1998; EU 1999; SETAC 1998, 1999; IUPAC 2003; IPCS 2002; Environment Canada, 1999). The consensus of the research is clear, that there is no evidence that humans have been adversely affected by ambient, environmental exposures to endocrine active substances and there is not convincing evidence of a growing human health issue. (Breithaupt 2004). In addition, the evidence in wildlife studies shows that some specific populations have been affected in areas of high contamination and exposure. As stated in the review of the International Union of Pure and Applied Chemistry (IUPAC), ". . . it is somewhat reassuring that after substantial research in the past decade, there have been no conclusive findings of low level environmental exposures to EAS

[2] Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). 2008. "Opinion on the Safety of Medical Devices Containing DEHP-Plasticized PVC or Other Plasticizers on Neonates and Other Groups Possibly at Risk." This report is available online at *http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_008.pdf.*

causing human disease" (*http://www.icsu-scope.org/projects/complete/endocrine execsum.htm*).

Question 13. Is there an established list of known endocrine disruptors?

Answer. No. In the U.S., under the Food Quality Protection Act (FQPA) of 1996, Congress required EPA to develop and implement a screening program—using validated test methods—to determine whether certain chemicals have estrogenic or other endocrine effects. Since then, EPA solicited advice from an advisory panel on what screens and what tests should be validated to determine whether chemicals have endocrine effects and then EPA began validating these tests. The issue which Congress put before EPA relative to testing for endocrine effects is much more complex than Congress appreciated in 1996, so the validation exercise has taken longer than anticipated. The mandate of the FQPA was on pesticide chemicals, so EPA has published a candidate list of pesticide chemicals for screening and testing in its Phase 1 of the Endocrine Disruptor Screening Program—but these are simply candidates for testing, not endocrine disruptors. EPA plans to begin ordering pesticide registrants and manufacturers to begin testing these chemicals for endocrine effects starting in August of 2008. Since these validated tests have not been applied yet, however, there is no established list of known endocrine disruptors in the U.S.

Question 14. Do infants and children have the same immune and endocrine system as adults? Do studies take into account these differences?

Answer, Do infants and children have the same immune and endocrine system as adults: Although the endocrine and immune systems of infants and children are composed of the same components as adults, these systems function in a manner that is somewhat different from adults. In all mammals, including humans, all organ systems develop, differentiate, grow and mature during development in the womb, during postnatal growth and throughout all life stages. Thus, the endocrine and immune systems differentiate during fetal development and grow and mature throughout childhood and adolescence. During puberty, the functions of the endocrine system change, becoming those of an adult. Similarly, the immune system grows and matures during childhood.

Studies of the potential toxicity of chemical substances specifically examine effects on the endocrine and immune systems to address questions of potential vulnerability during growth and development *in utero* and growth and development postnatally up to and including attainment of sexual maturation (and these include evaluation of reproductive function after puberty. Typical developmental toxicity tests evaluate the effects of exposures during organogenesis and histogenesis, those periods during which organ systems are differentiating, forming and growing *in utero.* In developmental tests, pregnant animals are treated with the test agent (thus exposing the offspring *in utero*) and then fetuses are evaluated just before parturition for effects on the skeletal and organ systems. The period that is covered by the developmental toxicity study is sensitive to induction of structural malformations (birth defects). Reproductive tests can include one, two or more generations. The purpose of these studies is to examine successive generations to identify possible increased sensitivity to a chemical, effects on the fertility of male and female animals, prenatal, perinatal, and postnatal effects on the ovum, fetus and offspring, including teratogenic effects, as well as perinatal and postnatal effects on the mother. In such tests, the males and females of the parental generation are exposed to the test substance prior to mating. Exposure of the parental generation (males and females) continues throughout the gestation and weaning periods (offspring continue to be exposed via their mother through lactation for test agents that are transferred into milk). After weaning, the offspring are placed on a direct exposure regimen. Exposure is continued through the stages of adolescent growth and development, and at the stage of sexual maturation, in multigeneration studies, the exposed animals are mated and the effects on reproduction are evaluated.

Scientists have long recognized that the endocrine systems and immune systems differ in younger mammals compared to adults. Such differences or "windows of vulnerability during fetal development and sexual maturation" are not a new concept, as these have been incorporated into research, testing and safety assessments for more than 40 years.[3] Reproductive toxicity testing is generally focused on deter-

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[3] Wilson J.G. Teratology Principles and Techniques. Chicago, University of Chicago Press; 1965.

[4] USEPA (U.S. Environmental Protection Agency). OPPTS Harmonized Test Guidelines Series 870 Health Effects Test Guidelines—Final Guidelines. 2007. Available from: *http://www.USEPA.gov/docs/OPPTS_Harmonized/870_Health_Effects_Test_Guidelines/Series/*.

[5] USFDA (U.S. Food and Drug Administration). Toxicological Principles for the Safety Assessment of Food Ingredients, Redbook. 2000. Available from: *http://www.cfsan.fda.gov/~redbook/red-toca.html*)

mination of the potential of a chemical to affect the ability of an organism to reproduce, while developmental toxicity testing focuses on the potential of a chemical to affect the viability or normal development of offspring of an organism during gestation. There are a number of standardized test methods that can be used to evaluate the effects of substances on development and reproduction.[4] [5] Reproductive tests can include one, two or more generations. The purpose of these studies is to examine successive generations to identify possible increased sensitivity to a chemical, effects on the fertility of male and female animals, prenatal, perinatal, and postnatal effects on the ovum, fetus and offspring, including teratogenic effects, as well as perinatal and postnatal effects on the mother. These studies require evaluations of all organ systems for abnormalities, including the endocrine and immune systems (specifically thymus and spleen).

With respect to endocrine disruption, within EPA's Endocrine Disruptor Screening Program (EDSP), the 2-generation mammalian reproduction toxicity test is the scientifically valid, definitive laboratory toxicity test for use in human health risk assessment of such substances. EPA accepts this test method as "valid for the identification and characterization of reproductive and developmental effects, including those due to endocrine disruption (ED) . . ." Therefore, for evaluating endocrine disruption, the chemicals that have completed such 2-generation mammalian reproduction toxicity test tests are viewed as having fully satisfied the needs for human health risk assessment purposes. In the EDSP, the 2-generation mammalian reproduction toxicity is often referred to as the definitive Tier 2 test for use in human health risk assessment. In EPA's EDSP, the Agency has clearly described the purpose and policy of such a Tier 2 Test:

> *Federal Register*/Vol. 63, No. 248/December 28, 1998/71554–71555 (emphasis added).
>
> The purpose of Tier 2 testing is to characterize the likelihood, nature, and dose-response relationship of the endocrine disruption of EAT in humans, fish, and wildlife. To fulfill this purpose, the tests are longer-term studies designed to encompass critical life stages and processes, a broad range of doses, and administration of the chemical substance by a relevant route of exposure, to identify a more comprehensive profile of biological consequences of chemical exposure and relate such results to the dose or exposure which caused them.
>
> *The outcome of Tier 2 is designed to be conclusive in relation to the outcome of Tier 1 and any other prior information.* Thus, a negative outcome in Tier 2 will supersede a positive outcome in Tier 1. Furthermore, *each full test in Tier 2 has been designed to include those endpoints that will allow a definitive conclusion as to whether or not the tested chemical substance or mixture is or is not an endocrine disruptor* for EAT [estrogen, androgen and thyroid] in that species/taxa.

Toxicological studies designed to explore potential reproductive and developmental effects are often designed to be multi-generational, which means they explore effects on an exposed rodent and one or more generations of its offspring.

Question 15. Have or haven't we seen many human studies on these chemicals? Is it even possible or ethical to conduct human studies?

Answer. With respect to human studies generally, all human subjects research that is considered by EPA—whether conducted or sponsored by the Federal Government or other entities—must follow the high standards embodied in consensus standards such as the Federal Policy for the Protection of Human Subjects, referred to as the Common Rule; the Guideline for Good Clinical Practice; the Declaration of Helsinki; and the Nuremburg Code. For obvious ethical reasons, humans are not typically dosed with compounds to determine effects. Most data regarding chemical effects is drawn from traditional toxicological testing (the proverbial "lab rat"). This data is sometimes augmented with human studies in the form of epidemiological data. Epidemiology is the study of the incidence and prevalence of disease in large populations and detection of the source and cause of epidemics of infectious disease.

Question 16. Usually chemicals are tested one at a time. However, we come into contact with numerous chemicals every day. Do these studies simulate real world exposures and what is the best way to test chemicals?

Answer. The question of exposures to mixtures of substances requires an understanding that humans encounter an ever-changing combination of natural and man-made chemicals at low levels, in normal, every day activities. We are exposed to a number of natural and man-made chemicals simultaneously and continuously every day. It is no surprise that they can be detected, and this should not lead to undue concern. Whether we are breathing air, which is composed of chemicals, or ingesting food, which is a complex mixture of chemicals, our bodies are absorbing a variety of chemicals every day. Scientists, physicians and others in related professions have

long understood that the actions of life are chemical by their very nature. As we interact with our environment, we are exposed to many thousands of chemicals, both natural and synthetic. The specific chemicals vary from day to day depending on our environment and activity. Generally, if a chemical is taken in by the body, it is either used or changed into a new chemical that can be used (nutrient) or it is altered by systems in the body and sequestered or excreted as waste. The increased sensitivity of analytical methods allows us to measure simultaneously more chemicals at lower concentrations in human tissues. This has led some to assert that the mere presence of chemicals in the body, or detection of mixtures of chemicals in the body, is harmful without regard for the amount of chemicals being referred to or the frequency or duration of presence in the body.

The presence of a substance that has adverse effects *at some level* does not imply that the presence of that chemical will lead to adverse effects *at all levels.* Potential toxicity must be considered in the context of the amount, route, duration and timing of exposure. For human health risks for chemical induced toxicity, evidence-based medicine and toxicology principles—the true scientific consensus—tell us that effects at high doses will not be realized at lower doses if the concentration falls below the target site threshold level. This principle applies just as much to "windows of susceptibility" during development as it does more broadly to all life stages. And it applies to mixtures as well as to a single chemical.

Our scientific understanding of how the body functions when exposed to environmental chemicals, and our knowledge based on current scientific methods for assessing harm posed by chemicals, indicates a large difference between low levels of exposure to chemicals and harm or disease resulting from exposure. *Potential harm must be considered in the context of exposure and inherent toxicity of the chemical(s)*—the amount, route, duration and timing of exposure and toxicity. Both naturally occurring and environmental chemicals—can be toxic at some dose. Indeed, many "naturally occurring" chemicals are potent toxins. The quantity of exposure—the dose—is of utmost importance in determining potential risk.

For example, one aspirin can be an effective therapeutic agent for a headache. Ingesting a full bottle of aspirin tablets will lead to toxicity. And taking an aspirin tablet and dividing into a hundred or a thousand equal parts, and then ingesting one of these small doses will not produce any effect whatsoever. This is a fundamental principle of biology and medicine and it applies to low level exposures to environmental chemicals, just as it applies to therapeutic agents and natural substances. The dose-response relationship for a specific chemical substance describes the association between exposure and the observed response (health effect). In other words, it estimates how different levels of exposure change the likelihood and magnitude of health effects. For many chemicals, there is a threshold below which an internal dose will not elicit a response. As the internal dose increases and exceeds the threshold, biochemical changes occur that may lead to adverse effects. There are clearly thresholds of exposures—doses that are so low as to cause no harm. Such doses below the threshold would not create any untoward risk whatsoever. For mixtures, this principle applies as well.

The human body is well equipped to manage low levels of chemicals. At low levels of many environmental chemicals, cells can act to break down and excrete these substances as wastes. However, when any chemical is present or accumulates to a toxic level, harm can occur. The same would apply for mixtures of chemicals. The question is not simply one of whether chemicals, natural or man-made are present in the body (a question of exposure), or whether the chemical can cause harm (a question of the chemical's inherent toxicity). Rather, it is the amount of those chemicals in the body relative to the amount that actually causes harm. In other words, the question is one of both exposure and toxicity. Therefore, it is the level and not the mere presence of any of the hundreds or thousands of chemicals in the body—regardless of their origin—that is important. This potential for harm relates to the concentrations of the chemicals in the body and their specific toxicity.

The standard battery of toxicity tests employed by the chemical industry includes specific tests on animals designed to address endpoints of concern to the health of humans, including children. This toxicity testing battery for industrial chemicals includes tests that have been specifically designed to evaluate endpoints that cover acute toxicity, hazards to development in the womb and to growth and reproduction, damage to cell components that could possibly trigger transformation into cancer later in life, and the potential of substances to produce adverse effects on all major organ systems, including the nervous system. This test battery specifically includes study designs to evaluate potential toxicity during the critical phases of development *in utero* and thus addresses concerns for any differential sensitivity of the developing organism during windows of development (these types of studies have been conducted routinely since the 1960s).

Animal model systems employed in standard toxicity testing routinely employ dose levels that are, 100-, 1,000- or even 10,000-fold higher than humans would be expected to experience. In fact, in order to provide assurance that potential toxicity will not be missed, the standard toxicity testing protocols for reproductive and developmental toxicity testing all require that the highest dose tested be chosen with the aim to induce some developmental and/or maternal toxicity but not death or severe suffering (*http://www.epa.gov/opptsfrs/publications/OPPTS_Harmonized/870_Health_Effects_Test_Guidelines/Series/870-3800.pdf*). While this approach is precautionary toxicology, because it ensures that there is little chance of "missing" a potential adverse effect, it also has the consequence of complicating communication efforts and precludes use of simple descriptors. Adverse reproductive or developmental effects observed at dose levels that produce parental toxicity may be secondary effects. If studies are conducted under conditions of overt toxicity, such effects may not be indicative of unique or selective developmental or reproductive toxicity. As a result, the only way to adequately communicate potential hazards of exposures is in a risk context. This means that the evaluative process must compare the dose-response data generated in the toxicity studies to estimated levels of human exposure to derive a margin of exposure (MOE). The MOE expresses the magnitude of the difference between a level of anticipated human exposure and the highest level at which there is no significant increase in the frequency of an adverse effect. This is critical information not only for assessing risk and considering risk management options when warranted, but also for communicating potential risks to the public.

Risk assessment methods have been developed, and continue to be researched and refined, to account for aggregate exposure (exposure to the same agent from multiple sources/routes) and cumulative risk (risk estimated for concurrent exposures to substances which act via the same mechanism).

Some specific risk assessment methods used and relied upon by U.S. EPA have been specifically designed for evaluating mixtures include:

Risk assessment methods for U.S. drinking water regulatory actions routinely account for exposures to a specific agent that may occur not only from drinking water, but also from other pathways outside of drinking water, thus affording adequate protection for all potential exposures. *http://www.epa.gov/waterscience/humanhealth/method/chapter4.pdf*.

> "The drinking water program usually takes a conservative approach to public health by applying an [relative source contribution] RSC factor of 20 percent to the RfD when adequate exposure data do not exist, assuming that the major portion (80 percent) of the total exposure comes from other sources, such as diet." *http://www.epa.gov/fedrgstr/EPA-WATER/2000/November/Day-03/w27924.htm*.

For over 15 years, risk assessment methods for hazardous waste site cleanup evaluations have routinely, included aggregate and cumulative quantitative calculations to account for both exposures to a single chemical from multiple pathways and concurrent exposures to multiple substances from the same or multiple routes.

> "To assess the overall potential for cancer and noncancer effects posed by multiple chemicals, EPA has developed Guidelines for the Health Risk Assessment of Chemical Mixtures that can also be applied to the case of simultaneous exposures to several chemicals from a variety of sources by more than one exposure pathway. Although the calculation procedures differ for carcinogenic and noncarcinogenic effects, both sets of procedures assume dose additivity in the absence of information on specific mixtures."
>
> Chapter 8, Risk Assessment Guidance for Superfund (RAGS), Volume 1, Human Health Evaluation Manual, Part A (1989) *http://www.epa.gov/superfund/programs/risk/ragsa/index.htm*"

With respect to experimental studies of chemical mixtures, many published interaction studies in toxicology are not interpretable for human health because they used faulty experimental designs, inadequate statistical methods or inappropriate biological model systems. Numerous interaction studies are not reliable for risk assessment due to a number of common problems: failure to characterize the individual dose-response characteristics of chemicals in a mixture; failure to test a no-interaction hypothesis; and failure to apply an appropriate statistical test to the data. For example, most individual chemical dose response curves are not linear. When testing a mixture of chemicals, an additive response can easily be mistaken for a synergistic response due to this non-linearity. The response predicted under the assumption of additivity must first be determined, followed by statistical comparison of observed vs. actual responses. (Borgert C.J. *et al.,* "Evaluating interaction

studies for mixture risk assessment." *Human and Ecological Risk Assessment,* vol. 7, pages 259–306, 2001.)

A Society of Toxicology panel has concluded that if toxicological data on chemical mixtures are to be relevant and useful for assessing risks to humans, it should be conducted at doses relevant to environmental exposures, including doses below the toxic threshold for individual chemicals. The scientific community has an obligation to demonstrate the clinical relevance of toxicological interactions of chemical mixtures to avoid the accumulation of "interactions" of doubtful relevance. (Teuschler L. *et al.* "Support of science-based decisions concerning the evaluation of the toxicology of mixtures: A new beginning." *Regulatory Toxicology and Pharmacology,* vol. 36, No. 1, pages 34–39, 2002.)

RESPONSE TO WRITTEN QUESTIONS SUBMITTED BY HON. JOHN F. KERRY TO STEVEN G. HENTGES, PH.D.

Question 1. Why are there such dramatically different results on the low-dose effects of BPA between the results of studies sponsored by the chemical industry and studies conducted by academics or government entities?

Answer. Scientific studies can only answer questions they are designed to answer. Studies sponsored by industry are typically, but not always, aimed at answering the critical question of whether a product is safe for use. These studies are generally designed to meet the requirements of internationally accepted test guidelines that were developed for this purpose. The studies are typically large in scale to be sure the studies have adequate statistical power and examine appropriate endpoints to address the question that the study is intended to answer. The studies are also typically conducted in highly qualified test laboratories under Good Laboratory Practices, which provides further assurance of the integrity of the study results.

Other studies, which can also include industry sponsored studies, are often aimed at other scientific questions that may or may not be directly relevant to assessing human health concerns. These studies may be limited in scope and examine endpoints that are difficult to interpret with respect to the safety of the substance being tested. Some studies, although scientifically well conducted, may have limited or no relevance for assessing human health concerns.

For bisphenol A, a very wide diversity of studies have been conducted and it is a gross oversimplification to say that studies sponsored by the chemical industry have opposite results to studies conducted by academic institutions. Very often, studies cannot be directly compared because they are so different.

As described in the answer to the question below, all relevant studies on bisphenol A have been systematically assessed in numerous weight of evidence evaluations. When all of the relevant data from these many studies are compared, in particular to determine whether the findings are repeatable or corroborated in independent laboratories, the most consistent result is that no effects from exposure to low doses of bisphenol A are reliably found. This conclusion is true even if the analysis is limited to non-industry studies. In that regard, studies sponsored by industry are consistent with the broader database and validate the overall conclusion that low doses of bisphenol A have not been reliably shown to cause adverse health effects.

Question 2. In light of dozens of advanced studies over the past several years, in conjunction with the recent assessment from the National Toxicology Program, do you believe that the Federal Government should control exposure to BPA?

Answer. Many hundreds of studies on bisphenol A have been conducted in the last 10 years and a substantial percentage of these studies were aimed at addressing the question whether bisphenol A could cause adverse health effects at very low doses. These studies are not all equivalent and, in general, they vary vastly in size, scope, quality and relevance to human health. The most comprehensive studies cover multiple generations of laboratory animals, are large in scale and statistically powerful, include a wide range of doses from very low to very high, and dose animals by the most relevant oral route of exposure. Other studies are small in size and scope, may be poorly conducted or reported, and dose animals by routes that are of little or no relevance to humans (*e.g.,* subcutaneous injection, direct injection into the brain). A further complication is that the results of these many studies are not consistent and show conflicting results.

When faced with a large and diverse body of data, as is the case for bisphenol A, scientists systematically evaluate the weight of scientific evidence to draw conclusions based on all of the available evidence. In recent years, numerous weight of evidence evaluations of bisphenol A have been conducted by independent scientific and government bodies worldwide. These evaluations consistently support the con-

clusion that bisphenol A is not a significant risk to human health, in particular at the very low levels to which people could be exposed through use of consumer products.

In addition to evaluating each available study on its own merits, a weight of evidence evaluation also assesses whether the findings of studies have been replicated or corroborated in independent laboratories, whether they are consistent within and across studies, and whether they are coherent when considered together. Repeatability is a fundamental principle of the scientific process; findings that cannot be replicated in robust studies cannot be accepted as valid.

Specifically in regard to the National Toxicology Program assessment, no serious or high level concerns were identified. Several possible health effects were identified as "some concern," which indicated that only limited and inconclusive evidence was available from laboratory animal studies and additional research is needed to determine whether the limited evidence is of any relevance for human health.

Based on the many evaluations that support the conclusion that bisphenol A is not a significant health risk, there is no apparent need based in science for action by the Federal Government regarding bisphenol A.

Question 3. Can consumers trust products that are currently labeled as "BPA-free"?

Answer. Bisphenol A is primarily used to make polycarbonate plastic and epoxy resins. Since neither of these materials would exist without bisphenol A, alternatives to bisphenol A effectively means alternatives to these materials. Presumably products labeled as "BPA-free" are made from alternative materials that are not made from bisphenol A.

To our knowledge, there are no alternatives that could easily substitute for all applications of these materials. In each case, a variety of factors must be considered to identify suitable alternatives and the critical requirements for each application vary considerably. For any alternative, two immediate hurdles are functionality (*i.e.,* the alternative must provide the function needed for that application) and safety (*i.e.,* the alternative must be safe for the application).

Compared to bisphenol A, no alternative has been so well tested or vetted so thoroughly by government agencies. Consequently, it is not likely that scientific data exists to support a claim that any alternative is safer than bisphenol A.

Whether consumers should trust products labeled as "BPA-free" must consider several factors including the veracity of the claim, the performance of the product, and the safety of the product. We do not have sufficient information on any of these factors to know whether consumers should trust these products.

Question 4. Why are low-dose effects of endocrine-disrupting chemicals like BPA more dangerous than those of other compounds?

Answer. The so-called "low-dose hypothesis" asserts that very low doses of endocrine-active substances may cause adverse health effects at very low doses. In particular, such low-dose health effects are postulated to occur with a non-monotonic dose-response, which means that health effects observed at very low doses would not be observed at higher doses. This hypothesis has not been scientifically proven and there is at best limited evidence that it could be valid.

A fundamental principle of toxicology is commonly expressed as "the dose makes the poison," which means that health effects observed at a particular dose will uniformly increase in intensity or severity as the dose is increased. Conversely, as the dose is decreased, a dose causing no effect can be found (a no-effect level) and any lower dose will also cause no effect. This is referred to as a monotonic dose-response (sometimes called a linear dose-response).

Toxicology studies are often designed to identify a dose at which no adverse effects. occur, which is referred to as a No-Observed-Adverse-Effect-Level (NOAEL). Doses below the NOAEL may not be tested since no adverse effects are expected. If the low-dose hypothesis is valid, health effects below the NOAEL might occur but not be found.

In response to the low-dose hypothesis, there are now a large number of studies on bisphenol A that examined low doses well below the accepted NOAEL. Most of these studies did not examine a sufficient number or range of doses to determine whether any dose-response is monotonic or non-monotonic and are thus not capable of validating the low-dose hypothesis.

It is important to note that the accepted NOAEL for bisphenol A is based on the most comprehensive studies, which were conducted over multiple generations of laboratory animals and included a wide range of doses from very low doses up to a very high dose above the NOAEL that induces toxicity. These studies do not validate claims that bisphenol A causes adverse effects at low doses and only monotonic

dose-responses were observed. These studies provide the most powerful evidence that the low-dose hypothesis, at least for bisphenol A, is not valid.

Beyond bisphenol A, the biological plausibility of the low-dose hypothesis is not supported by research on other endocrine-active substances. For example, two very robust and comprehensive studies have recently been published on estradiol and ethinylestradiol, the first being the prototypical naturally occurring estrogen and the second being the estrogenic substance commonly used in birth control pills. Both studies covered a wide dose range and neither study found non-monotonic dose-response for any observed effect. In comparison to these two substances, bisphenol A is a very weak estrogen that is 10,000–100,000 times less potent. No plausible explanation has been advanced to explain why bisphenol A would cause adverse effects at low doses with non-monotonic dose-response while more potent estrogens would not do so.

There is at best very limited evidence to support the validity of the low-dose hypothesis and very strong evidence that indicates the hypothesis is not valid. Lacking reliable evidence and biological plausibility, the low-dose hypothesis is just that—a hypothesis that has not been proven.

Question 5. In light of dozens of advanced studies over the past several years, in conjunction with the recent assessment from the National Toxicology Program, do you believe that the Federal Government should control exposure to phthalates?

Answer. Numerous U.S. Federal agencies charged with reviewing phthalate esters have done so thoroughly, and after taking exposures into consideration. Phthalates have been assessed by the Consumer Product Safety Commission (CPSC), the Food and Drug Administration (FDA), the Centers for Disease Control, the National Toxicology Program (NTP), the Cosmetic Ingredient Review (CIR), the European Union, and Health Canada, as well as other countries. Most notably, the CPSC assessed the safety of phthalates used in children's toys, using the primary phthalate (DINP) for that application as the focal point for review, and concluded that there is "no demonstrated health risk" to young children. The CPSC's review included consideration of exposure data drawn from studies of children's mouthing behavior. The FDA conducted a risk assessment of the main phthalate used in medical devices (DEHP) and concluded "the risk of not doing a needed procedure is far greater than the risk associated with exposure to DEHP."

Specifically in regard to the National Toxicology Program assessment, the NTP reviewed seven phthalates and concluded there was negligible to minimal concern for exposures to all the phthalate esters reviewed, except with respect to DEHP in certain situations. In particular, the only serious concern expressed was when used in medical treatment for critically ill male neonates. FDA responded to the NTP's review by cautioning that the benefits of medical treatment nevertheless outweighed the risks.

Based on the many evaluations that support the continued safe use of phthalate esters, there is no apparent need based in science for additional action by the Federal Government at this time regarding phthalate esters.

Question 6. What has been the experience of the European Union in phasing out phthalates in toys and childcare products? Has this been a significant logistical and manufacturing challenge for regulators and industry?

Answer. 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 science. Currently an array of other plasticizers are used in Europe.

Question 7. Why are low-dose effects of endocrine-disrupting chemicals like phthalates more dangerous than those of other compounds?

Answer. Low dose effects have not been claimed to be observed in testing of phthalate esters.

EA-FREE PLASTICS: THE ONLY ALTERNATIVE FOR SAFE PLASTICS *

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Non-Technical Summary

The Problem

Almost all plastics sold today release chemicals that have estrogenic activity (EA). While estrogens (the female sex hormones) occur naturally in the body, many scientific studies have shown that significant health problems can occur when chemicals are ingested that mimic or block the actions of these female sex hormones; the fetus, newborn, or young child is especially vulnerable. These health-related problems include early puberty in females, reduced sperm counts in males, altered functions of reproductive organs, obesity, altered behaviors, and increased rates of some breast, ovarian, testicular, and prostate cancers.

The Billion Dollar Marketing Band-Aid

Bisphenol A (BPA) and phthalates are two of thousands of chemicals that have EA that are in, and released from, almost all plastics sold today. The current commercial approach is to solve this health-related problem by producing BPA-free and/or phthalate-free plastic products. Unfortunately this incremental "marketing" solution to replace an individual chemical would not quickly (if ever) provide an EA-free health-related solution. Furthermore, chemicals or products substituted for BPA or phthalate-containing products often leach other chemicals having more total EA than the EA released by the original products.

Legislation to Date

The call to ban BPA and phthalates is growing rapidly. California has passed legislation banning phthalates and legislation to ban BPA is pending; similar bills are pending in Connecticut, New York, Pennsylvania, Maryland, Maine and Minnesota. The U.S. Senate is considering an amendment to the Consumer Product Safety Commission Reform Act that would ban phthalates. The European Union and Canada have already passed this legislation. However, all current legislation attempts to solve this EA problem by banning chemicals having EA one at a time. This approach is not an appropriate long-term solution because thousands of chemicals used in plastics exhibit EA, not just BPA and phthalates.

The Health-Related Solution

The most appropriate solution is to legislate that all plastics be EA-free, rather than ban specific EA-causing ingredients one at a time. This is not a pie-in-the-sky solution, as the technology already exists to produce EA-free plastics that also have the same advantageous physical properties as do almost all existing EA-releasing plastics. Some of these advanced-technology plastics are already in the marketplace.

Legislation to Date

- NY HB 11277: Bill introduced to the NY House of Representatives on May 27, 2008 that "Prohibits the manufacture, distribution and sale of toys and child care products containing bisphenol-A"
- Canada has announced plans to restrict the use of BPA, a chemical used to make hardened plastics. The government would prohibit the sale of baby bottles made with BPA. (*The ban will take effect mid-June*.)
- In April, the U.S. National Toxicology Program, which assesses the health effects of chemicals, also raised concerns about the potential "neural and behavioral" effects of BPA on all humans, but especially on fetuses, infants and young children. The program also warned against heating or microwaving food containers made with BPA, since some studies suggest that BPA may break down faster at higher temperatures.
- There will be a public telephone call-in line for the June 11–12, 2008 meeting of the NTP Board of Scientific Counselors. The meeting will be held at the Radisson Hotel Research Triangle Park, 150 Park Drive, Research Triangle Park, NC 27709 and videocast through the Internet at *http://www.niehs.nih.gov.libproxy.txstate.edu/news/video/live*.
- Senator Charles Schumer of New York and several of his fellow Democrats have proposed a ban on BPA in all children's products, and Representative John Dingell of Michigan is investigating whether the industry-backed studies that are

* Summary only the entire document is retained in Committee files.

used as the basis of the FDA's advice to consumers are really sufficient to warrant an all-clear for BPA.

- As part of his investigation, Rep. John D. Dingell (D–Mich.), Chairman of the House Energy and Commerce Committee, wants to examine the role played by the Weinberg Group, a Washington firm that employs scientists, lawyers and public relations specialists to defend products from legal and regulatory action. The firm has worked on Agent Orange, tobacco and Teflon, among other products linked to health hazards, and Congressional investigators say it was hired by Sunoco, a BPA manufacturer. Dingell has asked the Weinberg Group for all records related to its work in connection with BPA, including studies it has funded and payments made to experts. He cited a letter written by a company vice president in 2003 as Weinberg managed opposition in a long-running regulatory battle over a compound in Teflon. The letter said this strategy would be to discourage "governmental agencies, the plaintiffs' bar and misguided environmental groups from pursuing this matter any further."
- Last year, NIH convened two panels to help it analyze BPA risks. One panel, led by Fred vom Saal, Ph.D., Professor of Biology, University of Missouri (Columbia), consisted of 38 international experts on BPA who work for universities or governments. Last August, it found a strong cause for health concerns, including cancer and early puberty.
- In July of 2005, the European Union banned six different phthalates from use in toys and childcare items. The EU had already had temporary, renewable restrictions of these phthalates in place since 1999.
- In October 2007, California passed a law that would ban the sale or manufacture of toys containing phthalates, starting in January 2009.
- Japan, Mexico and Argentina, have also outlawed phthalates.
- China, which makes 85 percent of the world's toys, has developed two manufacturing lines, one for the European market and the other like-minded nations that ban phthalates, and another one for the United States and dozens of, mostly developing and Third World, countries that don't restrict them.
- In early March, Washington State passed a strict ban on phthalates in toys.
- The other states considering laws to ban phthalates include:
  - Connecticut
  - Hawaii
  - Illinois
  - Maryland
  - Massachusetts
  - New Jersey
  - New York
  - Rhode Island
  - Vermont
  - West Virginia
- In early March, the Senate passed a bill to reform the Consumer Product Safety Commission, that includes a ban on phthalates in children's toys. Lawmakers are working to reconcile the Senate measure with a slightly different version approved by the House of Representatives, which doesn't include the phthalate ban.

Technical Summary

Plastics are made by polymerizing a specific monomer in the presence of catalysts into a high molecular weight chain known as a polymer. The resulting polymer (usually in powder form) is mixed with much smaller, very specific, quantities of various additives (antioxidants, plasticizers, clarifiers, colorants, etc.) called a plastic formulation (usually proprietary) and then heated to form pellets. Plastic products are then made using processes (blow molding, extrusion, injection molding, thermoforming, etc.) that subject these pellets with more additives to various combinations of heat and pressure.

PlastiPure, and its sister corporation CertiChem, have extensive data showing that almost all existing commercially available plastics release chemicals that exhibit endocrine disruptor (ED) activity, especially estrogenic activity (EA) at concentrations (micromolar (~ppm) to nanomolar (~ppt) or even picomolar) that have many adverse biological effects, especially on fetal and newborn mammals, including humans. Endocrine disrupting chemicals (EDCs) having EA can have significant

deleterious effects at very low (micromolar to picomolar) concentrations, especially on fetal or developing mammals (NIEHS, 2006; EDSTAC, 1998; NRC, 1999; NTP, 2000; Welshons *et al.,* 2003; Kabuto *et al.,* 2004; vom Saal and Hughes, 2005; Swan *et al.,* 2005; Rubin *et al.,* 2006; vom Saal, 2006). This raises significant concern for human exposure because some plastic products, including baby toys, leach EDCs having EA at concentrations greater than this nanomolar to picomolar range (Takao *et al.,* 1999; Howdeshell *et al.,* 1999; Yang and Bittner, 2007).

Other than its products, PlastiPure has not yet identified any other commercially available plastic product which has been tested to be reliably EA-free [having no detectable EA according to the most sensitive available assays]. PlastiPure has not identified any other firm that is currently advertising EA-free plastics, although there are some firms which are marketing "Bisphenol A-free" or "phthalate-free" products (*USA Today,* 2007). *However, although they may not contain BPA or phthalates, PlastiPure's and CertiChem's data show that in normal use these products do release other additives (or monomers) that exhibit EA.* In fact, these data show that products advertised as BPA-free or phthalate-free plastics often release chemicals that have *more* total EA than the total EA released by products containing BPA or phthalates.

PlastiPure has developed an extensive line of technologically-advanced formulations and procedures for making safer plastics, food additives, and other products that do not release chemicals having EA. PlastiPure's unique formulations derived from its intellectual property, including one patent already granted (U.S. Patent # 6,894,093 B2) for some EA-free plastic formulations, and two pending patents. One of these pending patents is very broad and identifies many hundreds of plastic formulations to make many useful plastic products that in normal use would not release any chemicals having EA. This patent covers not only almost all monomers and all additives used in plastic formulations, but also most chemicals used in the manufacturing process to produce plastics that in normal use will not release detectable amounts of EA.

CertiChem has spent over 8 years and $5 million to develop the most sensitive and accurate assays available today to detect EA. PlastiPure has spent over $1.5 million in the last 8 years to develop plastics that do not leach any of thousands of chemicals having detectable EA, as measured by CertiChem's most sensitive assays. All PlastiPure plastics have also been developed to retain other useful properties of other plastics that do release chemicals having EA: flexibility, hardness, clarity, heat resistance, cold tolerance, UV tolerance, microwavable, etc. PlastiPure's advanced technologies use patent-protected state-of-the art advances in cell/molecular biology, endocrine physiology, polymer chemistry and polymer engineering.

That is, PlastiPure and CertiChem have used a set of advanced technologies to solve a health-related problem found in almost all currently marketed plastic items: they release one or more chemicals having detectable EA. Other firms have spent many millions to develop plastics that do not contain one or two of the thousands of chemicals known to have EA. Other firms are now spending many millions to billions to market those plastics that still release one or more of the thousands of other chemicals having EA. In contrast, PlastiPure has used advanced technologies to develop very broad health-related solutions to the problem of plastics releasing chemicals with EA, rather than market-related solutions that develop plastics that do not release specific chemicals having EA, but still release other chemicals having EA.

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