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OVERSIGHT ON EPA TOXIC CHEMICAL POLICIES

HEARING

BEFORE THE

COMMITTEE ON ENVIRONMENT AND PUBLIC WORKS UNITED STATES SENATE

ONE HUNDRED TENTH CONGRESS

SECOND SESSION

APRIL 29, 2008

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ONE HUNDRED TENTH CONGRESS
SECOND SESSION

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C O N T E N T S

OVERSIGHT ON EPA TOXIC CHEMICAL POLICIES

TUESDAY, APRIL 29, 2008

U.S. SENATE,
COMMITTEE ON ENVIRONMENT AND PUBLIC WORKS,
Washington, DC.

The full committee met, pursuant to notice, at 10 a.m. in room 406, Dirksen Senate Office Building, Hon. Barbara Boxer (chairman of the full committee) Presiding.

Present: Senators Boxer, Inhofe, Lautenberg, Klobuchar, Whitehouse, Barrasso, Craig

OPENING STATEMENT OF HON. BARBARA BOXER, U.S. SENATOR FROM THE STATE OF CALIFORNIA

Senator BOXER. The Committee shall come to order. We welcome our panel and our honored guests who are here today.

Today we will hear about the risks that toxic chemicals pose to our families and communities. Most at risk are children, pregnant women, the elderly and those who are ill. We will also hear some disturbing news about the White House and the Bush administration's efforts to corrupt EPA's toxic chemical risk assessment process. By placing politics before science, the Bush administration is putting the public in harm's way, this according to the GAO and EPA scientists.

A close look at the EPA's toxic chemical policies makes clear that improvement is necessary if we are to ensure that dangerous chemicals are properly regulated. EPA regulates toxic chemicals in the environment under several laws. The overall toxic chemicals law, the Toxic Substances Control Act, or TSCA, was adopted in 1976 and was supposed to help assure that toxic chemicals would be restricted or banned if they were hazardous.

But in essence, TSCA puts the burden on the Government to prove a toxic chemical is a risk. That is unlike the European program, called REACH. REACH puts the burden on the chemical industry, where it should be, to show that chemicals are safe.

In implementing TSCA and other laws like the Clean Air Act, the Safe Drinking Water Act and Superfund, EPA relies on risk assessments which evaluate how toxic a chemical is and to what extent people are exposed to it. In 1985, EPA developed a system called the Integrated Risk Information System, or IRIS, which establishes safe levels for toxic chemicals. The levels set in IRIS are used as the scientific foundation for most EPA regulatory programs and for many State programs to establish health standards for air and water pollution, waste cleanup and other programs. For exam-

ple, the levels set for arsenic in our water and benzene in our air went through the IRIS system.

Early in the Bush administration, the White House insisted on changing EPA does risk assessments. What they did is, they wanted to bring OMB, the Office of Management and Budget, and other agencies more directly into the process. Soon after EPA Administrator Johnson took over the agency in May 2005, he made changing IRIS and risk assessment a high priority. The GAO report I am releasing today criticizes the Bush administration changes to the risk assessment process and makes it clear that the danger faced by the public, when political interference and influence of polluters is paramount, is serious.

Under EPA's new approach, politics can be and already has been injected into multiple stages in the process. Now, no one can explain to me where there is room for politics when you are looking at the health and safety of the American people. Even worse, the new procedure effectively requires the White House, the Department of Defense, which contracts out much of its weapons programs, to agree with EPA on any risk assessment before it goes forward and before it is made public. So instead of having the scientists at EPA decide what is good for our health, we now have contractors essentially at the table. And we have the private sector and those with the special interests effectively at the table.

What makes it worse is, the entire process is kept secret, which GAO and EPA scientists say undermines the credibility of EPA's scientific assessments. That is because EPA scientists are being pushed aside by White House operatives and polluters. According to the GAO, the EPA's flawed risk assessment process essentially derailed the risk assessment for TCE, a solvent that is the most common organic groundwater contaminant in the U.S. TCE causes cancer, including childhood cancer, and birth defects. EPA's assessment for naphthalene, a component of jet fuel that the National Toxicology Program has found "can reasonably be anticipated to be a human carcinogen" has also been derailed. Naphthalene contaminates at least 654 Superfund National Priority List sites and many DOD facilities. GAO found that "DOD could face extensive cleanup costs" if naphthalene is more strictly controlled.

And here is the irony for me. This Administration has no end in sight for funding of the Department of Defense. And the Department of Defense protects us all over the world. Isn't it ironic, while they are doing that, they are derailing defenses against toxic chemicals? To me, it is the ultimate irony.

Similarly, GAO found extraordinary delays in the risk assessment process for formaldehyde—you have heard of formaldehyde—a chemical in plywood and many consumer products that has been linked to leukemia and other cancers. An EPA scientist with extensive knowledge of this program told our Committee staff that the Bush administration's risk assessment process could have "a significant impact on public health by delaying decisions so exposures can continue unabated to carcinogens, chemicals that cause birth defects and developmental effects, neurotoxic effects,

[so] a lot of people are affected."

This isn't about affecting a few people. This is about affecting our people in a broad way. And how many of us have said, children are our future?

This scientist also reported to us that "de facto, EPA can't go forward" without White House, DOD and other agency sign-off. The process has, according to this knowledgeable expert, put the scientists aside and has been "taken over by the White House," his words.

EPA's mission is to protect public health and our environment. Politics must never play a role when it comes to protecting our families. But as GAO has found, the series of delays has "limited EPA's ability to conduct its mission," and that is a direct quote from the GAO report.

The role of independent scientists at EPA must be restored so that EPA can carry out its mission without secret interference. We must also strengthen our toxics laws to ensure that chemical companies are responsible for proving that their products are safe, including safe for pregnant women, children, the elderly and others who are most vulnerable to toxic chemicals.

I so look forward to this hearing and hearing from our witnesses on this critical topic. And if you could give Senator Inhofe seven and a half minutes, please.

OPENING STATEMENT OF HON. JAMES M. INHOFE, U.S. SENATOR FROM THE STATE OF OKLAHOMA

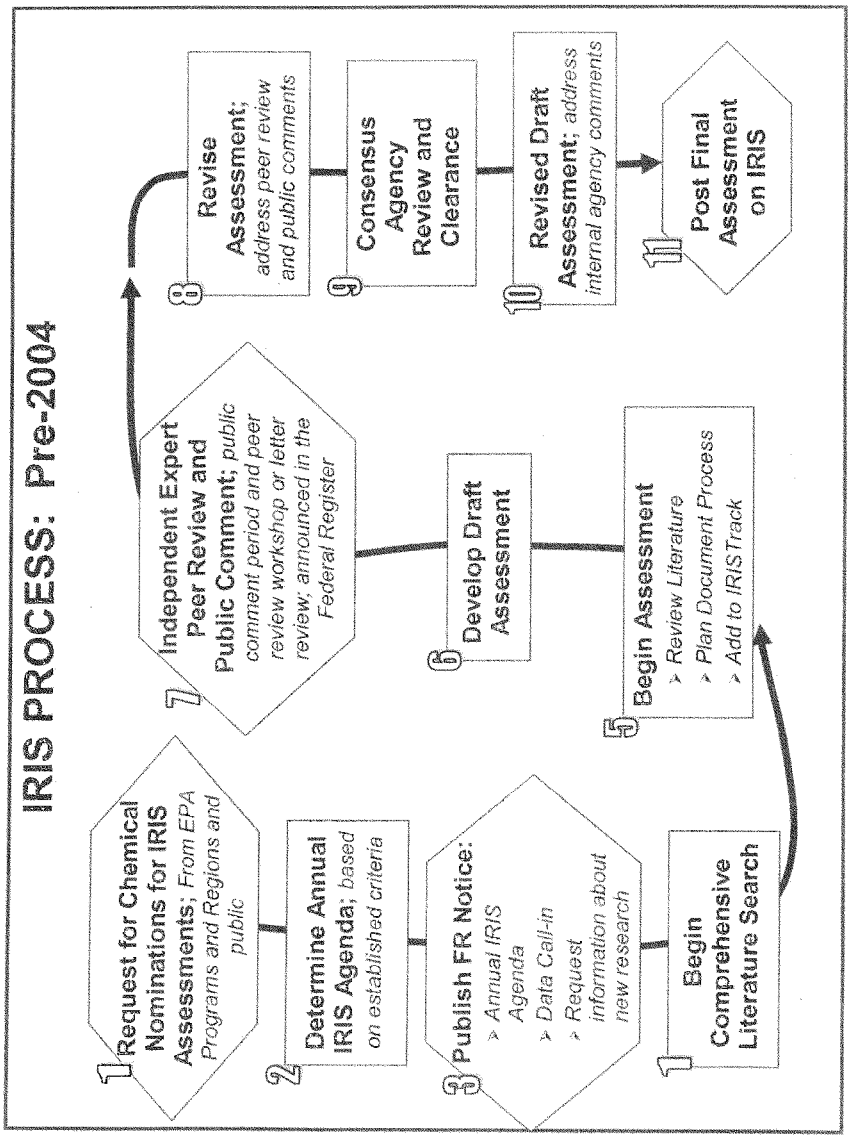
Senator INHOFE. Thank you, Madam Chairman. I don't need seven and a half minutes. I regret that I won't be able to stay here for the whole hearing.

Today's hearing concerns me for several reasons. First, it was called to take a look at EPA's chemical program under TSCA, at least that is what we were told and I think that is what the EPA was told. However, it now appears that a major part of the focus is on the changes in the IRIS program. Unfortunately, the witness whom the Chairman invited from the EPA, Assistant Administrator Gulliford, who runs the TSCA program, Assistant Administrator Gray runs the IRIS program. So Mr. Gulliford, while you might be able to offer some general comments on the IRIS program, you should not be expected to be the expert that you are in your own field.

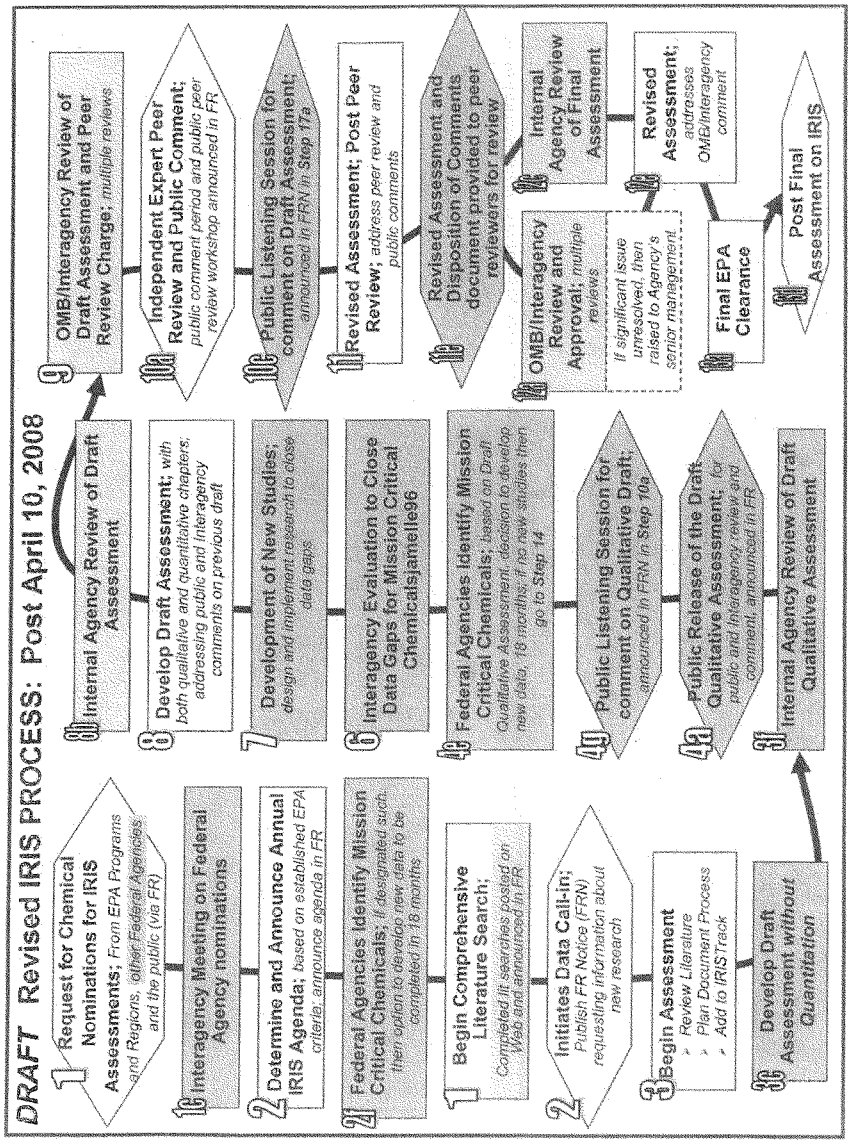
Next, my staff was repeatedly told by the majority staff that GAO was working on an IRIS report, but they weren't sure if it would be ready in time. This report, in keeping with our Committee rules, was distributed on Friday. However, we now understand that not only was the report completed by March 7th, but it was Senator Boxer's office that requested that the GAO embargo the report for 30 days. While this is occasionally done, Senator Boxer's deputy staff director went even further to request that the embargo be extended until this hearing. This is not a common practice and I have a letter from the GAO that I would like to enter into the record at this time.

Senator BOXER. Without objection, so ordered.

[The referenced material follows:]


IRIS PROCESS: Pre-2004
1 Request for Chemical Nominations for IRIS Assessments; From EPA Programs and Regions and public
2 Determine Annual IRIS Agenda; based on established criteria
3 Publish FR Notice:
Annual IRIS Agenda
Data Call-in
Request information about new research
1 Begin Comprehensive Literature Search
5 Begin Assessment
Review Literature
Plan Document Process
Add to IRISTrack
6 Develop Draft Assessment
7 Independent Expert Peer Review and Public Comment; public comment period and peer review workshop or letter review; announced in the Federal Register
8 Revise Assessment; address peer review and public comments
9 Consensus Agency Review and Clearance
10 Revised Draft Assessment; address internal agency comments
11 Post Final Assessment on IRIS

IRIS PROCESS: 2004 to April 2008
1 Request for Chemical Nominations for IRIS Assessments; From EPA Programs and Regions and public
2 Determine Annual IRIS Agenda; based on established criteria
3 Publish FR Notice:
Annual IRIS Agenda
Data Call-in
Request Information about new research
4 Begin Comprehensive Literature Search;
completed lit searches posted on Web and announced in FR
5 Begin Assessment
Review Literature
Plan Document Process
Add to IRISTrack
6 Develop Draft Assessment
7 Internal Agency Review of Draft Assessment
8 Revised Draft Assessment; address internal agency comments
9 OMB/Interagency Review of Draft Assessment and Peer Review Charge; multiple reviews
10 Independent Expert Peer Review and Public Comment; public comment period and peer review workshop announced in FR
11 Revised Assessment; address peer review and public comments
12 Internal Agency Review of Final Assessment
13 Final OMB/Interagency Review and Approval; multiple reviews
If significant issue unresolved, then raised to Agency's senior management
14 Final Agency Clearance Review
15 Post Final Assessment on IRIS


DRAFT Revised IRIS PROCESS: Post April 10, 2008
1 Request for Chemical Nominations for IRIS Assessments; From EPA Programs and Regions, other Federal Agencies, and the public (via FR)
16 Interagency Meeting on Federal Agency nominations
2 Determine and Announce Annual IRIS Agenda; based on established EPA criteria; announce agenda in FR
21 Federal Agencies Identify Mission Critical Chemicals; if designated such, then option to develop new data to be completed in 18 months
1 Begin Comprehensive Literature Search; Completed lit searches posted on Web and announced in FR
2 Initiates Data Call-in; Publish FR Notice (FRN) requesting information about new research
3 Begin Assessment
Review Literature
Plan Document Process
Add to IRISTrack
36 Develop Draft Assessment without Quantitation
31 Internal Agency Review of Draft Qualitative Assessment
4a Public Release of the Draft Qualitative Assessment; for public and interagency review and comment; announced in FR
4J Public Listening Session for comment on Qualitative Draft; announced in FRN in Step 10a
4g Federal Agencies Identify Mission Critical Chemicals; based on Draft Qualitative Assessment, decision to develop new data; 18 months; if no new studies then go to Step 14
6 Interagency Evaluation to Close Data Gaps for Mission Critical Chemicalsjanelle96
7 Development of New Studies; design and implement research to close data gaps
8 Develop Draft Assessment; with both qualitative and quantitative chapters; addressing public and interagency comments on previous draft
8J Internal Agency Review of Draft Assessment
9 OMB/Interagency Review of Draft Assessment and Peer Review Charge; multiple reviews
10a Independent Expert Peer Review and Public Comment; public comment period and public peer review workshop announced in FR
10c Public Listening Session for comment on Draft Assessment; announced in FRN in Step 17a
11 Revised Assessment; Post Peer Review; address peer review and public comments
12a Revised Assessment and Disposition of Comments document provided to peer reviewers for review
12 OMB/Interagency Review and Approval; multiple reviews
If significant issue unresolved, then raised to Agency's senior management
12g Internal Agency Review of Final Assessment
12e Revised Assessment; addresses OMB/interagency comment
13 Final EPA Clearance
16 Post Final Assessment on IRIS

Senator INHOFE. My concern in all this, inviting the wrong EPA witness, withholding from the minority the GAO report for more than 50 days, is that this hearing today appears to be set up as a "gotcha" hearing to try to embarrass the Administration, instead of a legitimate oversight hearing. If the Chairman were truly concerned about oversight and changing policy, then she would have shared the report when it became available over a month and a half ago, and she would have invited the correct EPA witness. I understand at one point she wanted the Administrator, but she invited the TSCA Assistant Administrator.

Oversight works best when it is done in the open. By not disclosing the true intent of today's hearings to the agency and the minority, we are left with, at best, an incomplete and inconclusive attempt at oversight.

I believe we need to work together on oversight, such as a hearing examining the ethanol program. This Committee has not held such a hearing, despite massive changes in the law last year, which has increased food prices contributing to riots. And by the way, I would like to make that as an official request. I am going to be on the floor today, Madam Chairman, at some length, talking about the mandates, the ethanol mandates and how they relate to the cost of food stocks. In fact, this is an area where I will be in concert with what normally are not my best friends on the environmental issues. It is something I think you agree with, that I think we need to determine, be concerned about this diversion of these to fuel from food.

So I would like to make that request, I think we should have that. I will be more elaborate on the floor in talking about this, I have about a 1-hour speech on the ethanol mandate and how much that is hurting a lot of people.

Thank you, Madam Chairman.

[The prepared statement of Senator Inhofe follows:]

STATEMENT OF HON. JAMES INHOFE, U.S. SENATOR
FROM THE STATE OF OKLAHOMA

Good morning. Today's hearing is to examine the adequacy of the mechanisms for the evaluation and regulation of chemicals by the EPA. The subject is important because the chemical industry is a crucial part of the US economy and we have to be mindful of what we put at risk if we over-regulate this industry and stifle its 30 year history of innovation.

Here are some statistics. The United States is the No. 1 chemical producer in the world, generating $635 billion a year and putting more than 5 million people to work. The US chemical industry paid more than $27.8 billion in Federal, State and local income taxes in 2006. More than 96 percent of all manufactured goods are directly touched by chemistry.

But it is about more than money. Chemicals are the essential building blocks of products that safely and effectively prevent, treat and cure disease; ensure the safest and most abundant food supply in the world; purify our drinking water and put out fires. They are the foundation for life-saving medical devices, such as sutures, internal tubing, and scalpels. Innovations in chemistry have made planes, fighter jets, and space shuttles safer and more secure. Plastics are used to make lighter, yet stronger, cars and silica is an ingredient in low-rolling resistance tires, all of which increases automobile fuel efficiency. Alternative sources of energy, on which cap and trade proponents are relying, are dependent on chemicals. Wind power blades contain polyester and resin additives and solar power relies on silicon-based materials. Finally, chemicals keep our children and our men and women in uniform safe by increasing the effectiveness of child safety seats, bicycle helmets, and Kevlar vests. I could go on and on.

The reason I point all this out is that there are many people who come to this hearing with a belief that the US chemicals management program is broken and that Congress needs to completely rewrite the Toxic Substance Control Act (pronounced TOS-KA). I do not agree.

For nearly 30 years, chemical products have been among the most thoroughly evaluated and regulated, covered by more than a dozen Federal laws, including TSCA. These statutes call for regulation of chemicals based on risk. I do not believe American chemicals innovation should be stifled by government regulation without the clear identification of risk. We need to ensure that we regulate chemicals based on demonstrated risk not the just the perception or assumption of it. That "precautionary" concept is one that I cannot support.

There are also those who have expressed concern over EPA's risk assessment practices. I am one of them. I have long been concerned about the lack of transparency and participation inherent in EPA's risk assessment process, as well as how risk is communicated to the public. I was pleased with EPA's recent changes to the Integrated Risk Information System. These changes allow the public to be involved in the risk assessment process sooner. Now, environmental groups, scientists and the regulated community can provide data, research and comments on risk assessments before they are finalized. Additionally, there is now a concerted outreach effort to members of the scientific community and more rigorous peer review. I understand that there are those on this committee who believe this is somehow stifling EPA scientists or putting politics into the scientific process. But I don't understand how someone can stand up and say they support public right-to-know, scientific community participation and transparency when the Agency makes regulatory decisions but not support those very same principles when it comes to risk assessment. More science means better decisions; more defensible decisions.

As I said 2 years ago during a toxics oversight hearing I held when I was Chairman, there is no shortage of strong feelings when it comes to chemicals and how they are regulated and managed. I look forward to hearing from our witnesses today and perhaps we will continue to uncover implementation problems that this committee, exercising its oversight, can encourage the Agency to rectify.

Senator BOXER. Thank you.

I am going to just use the privilege of the Chair just to respond to say that I don't mind your attacking me on this. We certainly did tell your staff that IRIS was a very important part. The reason, we really wanted Administrator Johnson here, because we think the buck stops there. But we also believe that TSCA and the role of TSCA is very important, even though the law has been weakened. This is bigger than just the IRIS program. It really is about all of our laws that rely upon risk assessment. But I don't mind that you are unhappy with me. This is certainly not going to be the last time.

Senator INHOFE. Oh, I am not unhappy with you, if you would me respond.

Senator BOXER. It is not the first and it won't be the last. But I just want to say this. For me, the most important thing, and I am sure it is for you, is not getting into an argument about the date of the GAO report and all that. We obviously wanted to understand it, read it and do the rest. But it was the report we had asked for.

But what is important is the bottom line here, which is that we are being told, and this is a scandal, frankly, that our families are being put at risk because politics has entered the process of these risk assessments. And this is too important for us to bicker over how many days we told you this, that or the other.

But I am happy to hold another hearing on this, and you would have every right to call whomever you want, and I would be delighted to do that at any time. But I really do want to thank you for being here, I know you have a hectic schedule.

Senator INHOFE. Let me clarify, I certainly did not attack you, nor would I attack you, nor will I. But on this, I think if we do ask for am embargo, which can be very appropriate if we share that with each other, it would be a better idea.

Senator BOXER. Yes, as you say, it has been done before, and I will.

All right. Senator Lautenberg.

OPENING STATEMENT OF HON. FRANK LAUTENBERG, U.S. SENATOR FROM THE STATE OF NEW JERSEY

Senator LAUTENBERG. Thank you, Madam Chairman. How nice it is to start off this spring day with a discussion of not the issues but the format or the process. And I think that if one attempts to hide information, the biggest obfuscation took place when we said that global warming is a hoax. And that tried to hide the effects and the seriousness of what that condition was ultimately is now, in front of our eyes, almost daily on TV and news, news delivery systems.

So this is the kettle and the pot being called black. And Madam Chairman, I know you don't need it, but stay strong on these things. Don't let yourself be cowed.

Senator BOXER. I make you that commitment.

[Laughter.]

Senator LAUTENBERG. Earlier this month we held a hearing on a matter that is still on many Americans' minds, the impact of contaminants in our Nation's water supply and the health hazards that they may pose to our residents. These contaminants include chemicals that are used in rocket fuel, gasoline additives proven to have negative effects on people's health. The real problem with our water supply is the lack of regulation by EPA. When it comes to regulating the industrial chemicals that are used in thousands of everyday products, from plastics to children's toys, the EPA is missing in action. The absence of EPA regulation is putting people at risk.

For instance, scientific studies show a potential link between a chemical called Bisphenol-A, which is used to make baby bottles and water bottles and a host of medical problems, including cancer and reproductive issues arise. But here is the worst part. While the chemical is being developed and then used in the products we rely on, the EPA did nothing. Instead of speaking out for our health, they were silent. And the agency was not just silent about this single chemical. Out of the 80,000 chemicals used now to produce the products they have found throughout our homes, the EPA has only tested 200. It is unacceptable.

I refuse to let my grandchildren become the newer version of the canary in the coal mine when it comes to determining which chemicals are safe and which are not. We need to change the system so instead of passively waiting for a chemical to hurt somebody, we prove that it is safe before it gets into the hands of the consumer.

That is why I will soon introduce an updated version of the Kids Safe Chemical Act. Chairman Boxer supported this critical bill when we introduced it during the last Congress, and I hope we are going to be able to work together on it again this year. This legislation would direct the EPA to make sure that every chemical in

every product is safe before it winds up in the hands of the consumer.

We already regulate pesticides and pharmaceuticals this way. It seems to me just common sense that we do the same thing for industrial chemicals that are used in everyday consumer products. I believe that it is, and I believe that the American public will agree. I look forward to working common sense back into our environmental laws to make sure the products we rely on every day are safe.

Madam Chairman, as we approach the spring and we think about when it was that Rachel Carson started the anti-pollution movement, it was 1963, and it was the book called Silent Spring. It produced an anxiety, produced a tension to what we were doing to ourselves, particularly at that time with DDT. It took 9 years for that material to be obliterated from use and its presence.

So this is the place and this is the time, Madam Chairman, that we have to get on with these things, stop talking about them and do something about them. Thank you very much.

Senator BOXER. Thank you very much. And Senator, I would be very honored to be the lead co-sponsor on your legislation, because I think it gets to the heart of the matter.

Senator BARRASSO.

OPENING STATEMENT OF HON. JOHN BARRASSO, U.S. SENATOR FROM THE STATE OF WYOMING

Senator BARRASSO. Thank you very much, Madam Chairman.

Madam Chairman, we do need to protect our children, no matter what age, from the effects of harmful chemicals. I doubt there is anyone in this entire room today who wouldn't support that goal. There is nothing we wouldn't provide for our children. Children need safe drinking water, life-saving medicines and safe food to eat.

One question we might ask ourselves in this hearing is the following: has the chemistry industry and the EPA, under the Toxic Substance Control Act, helped improve the lives and the health of our children? To answer that, I would like to highlight an article that ran on Thursday in the Washington Post, a front page article, and the story is entitled For Children, a Better Beginning: Study Finds Progress on an Array of Issues from Birth to Age Ten.

In brief, the article says, in a wide-ranging look at how children have fared in their first decade of life, there is a promising picture of American childhood. Sixth graders feel safer at school. Reading and math scores are up for 9 year olds. More preschoolers are vaccinated. Fewer are poisoned by lead.

The analysis, which created a composite index of more than 25 key national indicators, reports an almost 10 percent boost in children's well-being from 1994 through 2006. It goes on to say that, for example, the mortality rates for children ages one to four has declined by a third. With lead, the study reported a striking decline in the percentage of children younger than six who have elevated lead levels in their blood. The article mentions possible reasons for this trend, that is improved health and conditions, better Medicare care, better nutrition, mandatory use of seat belts, safer playground equipment.

What role has the chemical industry played in providing better medical care, car seats and safer playground equipment and so on? I think there is a role. Chemistry, using chlorine, plays a role in producing 93 percent of the top-selling medications in the United States. Children benefit from some of these drugs, including those that treat epilepsy, asthma and depression. The antibiotic Vancomycin, with which I am very familiar, which is made with chlorine chemistry, has saved the lives of patients suffering from serious, stubborn bacterial infections.

Chemicals make prosthetic devices used as polyvinyl chloride, or PVC, which is a common chlorine-containing plastic used to construct prosthetic legs and arms for children who lose their limbs or have birth defects. Thanks to these devices, many of these children can lead normal lives and participate in most activities.

PVC is used to make blood bags, IV fluid bags and tubing to deliver needed care to young patients. Incubators for prematurely born infants are constructed of these same plastics. The chemical industry also makes the plastics used to manufacture child car seats, safer playground equipment.

That is not to say that it is a completely rosy scenario for today's children. There are still areas of concern, such as increased rates of childhood obesity and also low birthweight babies. So we must be ever-vigilant. We need a strong and viable regulatory framework, the same framework under TSCA that has spurred advancements to help our children, not gotten in the way of it. This framework can provide the next series of advancements that can make the future better for all Americans.

We must not enact policies that hamstring new chemical development that would prevent these new advancements. Otherwise that next child vaccine, the next bike helmet, the next prosthetic leg, will not be there if our families need it the most.

TSCA has helped establish EPA as a leader around the globe in developing the tools we need to understand chemicals. It is a flexible statute that allows the EPA the ability to vary its assessments of new chemicals, according to the attributes and the expected uses of each substance. The framework ensures that the majority of new chemical substances pose little to no risk to our health or to the environment. Every chemical at a certain exposure is toxic. Fluoride used in toothpaste and purposely put into our drinking water, if ingested in massive amounts, can cause harmful health effects. As they say, the dose makes the poison.

My point is that we don't need to scare folks about risks that are not there or of a low probability. That is why we need a statute that realizes the differences between risk of exposure and toxicity. Is TSCA perfect? No. Could there be room for improvement? Perhaps. Could the implementation of the current Act be improved? Absolutely.

GAO released a report in 1997 that made recommendations for improvements. Many of these need to be implemented, in particular, recommendations for improving the use of confidential business information, prioritization of chemicals for risk evaluation, reducing some of TSCA's administrative burdens relating to chemical testing requirements and improving and validating the models EPA uses to assess and predict the hazards of chemicals.

With that, Madam Chairman, I welcome the witnesses and look forward to the testimony. Thank you, Madam Chairman.

Senator BOXER. Thank you.

I just would like to put in the record, without objection, a list of toxic chemicals that have been regulated under the IRIS program. That is why our kids, that is certainly a strong reason why we are seeing some good news on our kids. But what the White House is trying to do is change it, is bring politics into it. So we had, for example, under IRIS, we have had regulations about arsenic, mercury, cyanide, toluene, chlordane, DDT, PCBs, it goes on and on, many chemicals with very long names.

The bottom line is, the purpose of this hearing is, we don't want to go backward. Some of us want to make it even stronger, not to hamstring our companies from making prosthetics, I don't know where that comes into it, to be honest with you. We are talking about protective standards in our water, in our air, not in prosthetics. So let's not raise false issues.

So let me just be clear about what today is about. What we have learned is that this program that has in fact made our kids safer is in jeopardy. As a matter of fact, the Administration claims under their new way of doing things, which they are now institutionalizing or trying to, that they would take care of 50 chemicals? Fifty in 1 year?

Male Speaker.

[Remarks off microphone.]

Fifty. And they did two. So that is the purpose of this hearing.

[The referenced material was not received at the time of print.]

Senator BARRASSO. Madam Chairman, not to be argumentative——

Senator BOXER. You can be.

Senator BARRASSO. Pardon me. The plastics that I have seen as an orthopedic surgeon for 25 years that have been used to build the prosthetics are advances in plastics, and they are chemically related. That was my point.

Senator BOXER. You are right. But we are talking about regulating these chemicals in water and air. We are not talking about regulating them for prosthetics. We are not talking about banning them. We are talking about regulating them, so that kids don't breathe them, drink them, play in them on Superfund sites and the like.

So we are talking past each other. Nothing that you said do I object to. I am not suggesting that these be banned for prosthetics or anything else. I am saying we need to control these when scientists tell us they are going to cause birth defects, they are going to cause cancer. That is what we are talking about.

Senator WHITEHOUSE.

OPENING STATEMENT OF HON. SHELDON WHITEHOUSE, U.S. SENATOR FROM THE STATE OF RHODE ISLAND

Senator WHITEHOUSE. Thank you, Madam Chair.

I just want to express my appreciation to you for holding this hearing. I think it is an important hearing. We have north of 80,000 chemicals to which American families are exposed, very few of them are tested for safety. In the program that currently exists

the burden of proof is on the regulators to show that they are unsafe, which makes the balance really in favor of industry rather than in favor of families.

There is increasing awareness of health risks that these chemicals can cause. Unfortunately, we are also operating in an environment in which the Bush administration record on environmental and public health issues gives very much the impression of being not a part of the progress that Senator Barrasso described, but a counter-weight to the progress that Senator Barrasso described.

EPA itself has too often been in the way of public protection, as we have seen, with particularly the CAFE standards and waiver. That is the most prominent. But over and over again there are cases, and on the occasions when the EPA does stand up for American families who face these health risks, then the Administration has put OMB in the role of being sort of the Administration hit man to knock those down.

So I think there is a legitimate concern that the procedures that the Government Accountability Office has addressed in its report may stack the deck further against American families who don't have the expertise to make this kind of determination and are relying on the Government to help provide them with a safe environment.

So I think it is a great hearing, I am glad that you have called it and I look forward to hearing from the witnesses.

Senator BOXER. Thank you, Senator, and I appreciate your leadership on oversight of EPA in general. You have been very strong on that, so we thank you very much.

Senator CRAIG.

OPENING STATEMENT OF HON. LARRY CRAIG, U.S. SENATOR FROM THE STATE OF IDAHO

Senator CRAIG. Thank you, Madam Chair.

Well, I am sitting here listening trying to determine whether this is a TSCA hearing or an IRIS hearing, but I will assume that it is the politics of chemicals. Probably that is a broader premise to the issue at hand. If you are going to talk about the politics of chemicals, and that is legitimate, you also have to talk about the importance of chemicals in our society today and what they have done for society, along with what they have done to damage society in one form or another. Those are all phenomenally legitimate criteria for an oversight hearing.

And Madam Chair, I am sorry, I am going to err on the side of a doctor today and not a politician. I am going to err on the side of Dr. Barrasso and his statement because I think it was overreaching in the broad sense, not overreaching, but it reaches out in the broad sense to talk about striking balance and assuring quality human health in our Country.

Our history is replete with the lack of knowledge and understanding as to the application of or the pollution of chemicals into our environment. And when we found it out, when we knew it, we began to move. From the very loud cry of Silent Spring, as one Senator mentioned, to what we have done effectively with TSCA, which is today a responsible model of public policy that works and brings about that kind of balance.

My great fear is not unlike what we are experiencing today in the petrochemical industry. When we didn't do it they did it, meaning somebody outside our Country. And now we are being victimized because we weren't smart enough to continue production in our Country and do it in a clean and responsible and environmentally sensible way.

How many times this year has our society been warned about a product coming in from outside our Country that might in some way injure human health? The more we regulate in ways that are punitive, that deny a reasonable entry into the market based on sound science, the more someone else is going to do it offshore. The beauty of what our Country has always done historically is its phenomenal transparency, not just for us and our consumer when the knowledge base was there to do so, and a good regulatory process produces that knowledge base, but at the same time it was transparent to the rest of the world.

TSCA's importance is directly tied to entry into manufacturing, processing, importing, and the use and distribution in commerce as it relates to how we regulate chemicals. Let us also recognize the value of the industry itself to the economy of our Country. It just so happens that it is about a $635 billion industry. We represent 22 percent of the world's economy as it relates to the chemical industry. And we are rapidly shoving it offshore by cost of input and cost of regulation. That shouldn't happen. We ought to continue to lead in that area, and we are not talking about just minor jobs, we are talking about jobs in the industry that average $50,000 and above, a very important industry to our Country.

So fair and balanced oversight, absolutely, Madam Chairman. Political forum, shouldn't necessarily be that, although I am not so surprised that it has become that. Our job is oversight to see whether TSCA is working, whether IRIS is working. If it isn't, then we ought to make it work. More importantly, we ought to make it work in concert with what the rest of the world is doing to make sure we do it better, more cost-effective, at the same time with a sensitivity to human health that is paramount.

It is kind of like where we are today, Madam Chair, with energy. If it isn't clean and if it is an emitting source, we don't want it any more. We are driving our energy economy into cleanliness. We ought to do the same thing with the petrochemical industry. And that isn't run them offshore, invite them to stay in a criteria of public policy that allows them to prosper and provide safe products for the consumer. That is our job. We can make it as political as we want to or we can be reasonable and responsible. I would guess the public in the large would want us to be the latter instead of the former.

I thank you and look forward to the testimony.

Senator BOXER. Thank you. I feel compelled to respond, since my name was invoked, Madam Chairman, several times.

No. 1, it is not our job to keep the chemical companies at the table. It might be in another committee. This is the Environment and Public Works Committee. The EPA has a job to protect public health. When it comes to the profitability of the chemical companies, let's take that up in the Commerce Committee. Let's look at that. Yes, but not as a criteria here. Our job is very straight-

forward, and that is protect our people from harm, from chemicals, toxics. And if we hadn't been doing it, all those statistics that Dr. Barrasso, if I might say, has cited, wouldn't be there.

Now, you have taken your stand with Dr. Barrasso. Now, he is an orthopedic surgeon and I am really honored to have him on this Committee. On the panel today, we will have a pediatrician and we will have an Ob-Gyn. In EPA, we have many scientists whose job it is to protect the public. So while we all need to be listened to, I have other credentials. I am a grandma, I bring those proudly to the table.

But the fact of the matter is, the people who know about this are the people who are experts in toxic, are the people who see pregnant women, who are warning them about the toxic chemicals that are unfortunately ever-present.

I also want to make one last point here, which I think is important. There seems to be all this "confusion" about this hearing. Let me tell you the title of this hearing today, no confusion, "Oversight on EPA Toxic Chemical Policies." Policies. That means anything and everything is on the table. We can look at IRIS, we can look at TSCA.

But politics shouldn't be played when it comes to protecting the health of our families. That is one of the reasons we have this hearing today, because politics is being played when you have the White House suddenly turning its back on the science and the EPA and inviting to the table, through various agencies, the special interests. That is not what should be happening when it comes to protecting the health of the people.

And I am a little stunned that my colleagues on the other side of the aisle aren't working with us on this, because you love your kids and grandkids as much as I love mine, and you would throw yourself in front of a truck for them. Well, we may have to throw ourselves in front of a train for them here, because there is a train leaving the station with Administrator Johnson on it and President Bush's OMB on it, trying to derail a very important risk assessment program that has at least done something good to keep our children safe. If this is going to go forward unchallenged, we are going to see a slowdown and a delay. And everyone says that, including the GAO. We are harming our children.

Senator BARRASSO. Madam Chairman, since my name came up——

Senator BOXER. Well, we are not going to start that, but I will go back to you after we, for the first round of questions.

Senator KLOBUCHAR.

Senator KLOBUCHAR. Thank you very much, Chairman Boxer. Thank you for holding this hearing.

Just listening to Senator Craig, I just view our role as one of oversight, that is correct. But it is also oversight of enforcement. I come at this not only as a mother who, when you think first hand of these baby bottles and things like that could have toxic chemicals in it, it just hits you hard, but also as a prosecutor. I have always learned you can have strong laws and politicians can stand up and make credits about laws. But if you don't have the enforcement angle and you don't have people watching over to make sure that these laws are being enforced, then we are not doing our job

and Congress has to come in. I believe that is what we are trying to do, is to figure out what is going on here.

I come at this not naively but as someone that looks at this, look what happened with these toys. Who would have ever thought, and I don't think anyone would believe that people want to allow AquaDots to morph into date rape drugs in this Country, and that is what happened here. That is what happened. They weren't, our Country, our Consumer Products Safety Commission, wasn't watching over these toys and they came into our Country, and they shouldn't have. And this happened again and again and again, and finally Congress had to step in, when the Administration did not, and say, we need more tools, what do you need to enforce these laws, we will help you. What do you need? A better statute on the book? We will help you. And that is what happened in the last year in this Congress.

So it doesn't surprise me at all that we might have to get involved in these toxic chemicals. And I was shocked to read in this hearing the testimony of Ms. Annette Gellert, who is going to be testifying on the second panel, and I am not going to be able to be there for that, because have a Commerce hearing on the mortgage crisis going on at the same time. But I read about how she had blood tests done on herself and her daughter, and out of 70 toxic chemicals they tested for, they found 36 in the mother and 34 in the daughter. You figure as a mother that you are supposed to be able to provide your child with a safe environment and you do your best, and then you find that things outside of your control are coming into your home.

I figure that in a Country with as many resources as ours, there is no reason that people should have to get their safety information from news stories or from people that are already sick in the hospital. That holds true not just for the EPA, but across all Government agencies, whether we are talking about the spinach weed, the pet food that we get or the drain at the community pool. These are all things that have gone on in this Country in the past year.

So I am looking forward to hearing from our witnesses, Mr. Stephenson from the GAO, about how the Toxic Substance Control Act is being controlled, where the weaknesses have been and what we can do better to give Americans the sense of safety that they deserve. Thank you very much.

Senator BOXER. Thank you, Senator.

So we will start our panel first with James Gulliford, Assistant Administrator, Office of Prevention, Pesticides, and Toxic Substances, to be followed by Mr. John Stephenson, Director, Natural Resources and Environment, from the General Accounting Office, who did this report.

Mr. GULLIFORD.

STATEMENT OF THE HON. JAMES GULLIFORD, ASSISTANT ADMINISTRATOR FOR PREVENTION, PESTICIDES AND TOXIC SUBSTANCES, U.S. ENVIRONMENTAL PROTECTION AGENCY

Mr. GULLIFORD. Good morning. I appreciate the opportunity to share with the Committee our progress to date as well as new efforts underway to protect human health and the environment from the adverse effects of chemicals as authorized under the Toxic Sub-

stances Control Act. TSCA provides EPA with the authority to review and manage risks from new chemicals and to collect health and safety data as well as production, use, and exposure information on industrial chemicals.

We use sophisticated models to assess chemicals, we facilitate pollution prevention and we implement voluntary programs to support our regulatory framework. We work closely with the domestic and international community. As an example, we have collected health and safety data on 2,200 high production volume chemicals which cover more than 93 percent of the organic chemical production volume. EPA has also successfully used TSCA to bring about the phase-out or significantly reduce the production, use or release of various chemicals, including PFOS, PFOA and other priority chemicals. There are many more accomplishments detailed further in the written testimony I have submitted.

Overall, while no law is perfect, TSCA provides broad authority for the agency to adequately control new and existing chemicals and to address emerging chemical issues as they arise. As I said, while there are real accomplishments, we know there is more to be done. So this past August, the countries of North America came together to accelerate and strengthen the management of chemicals in North America. This new effort we now refer to as ChAMP, the Chemical Assessment and Management Program.

We believe these efforts will significantly improve what we know about industrial chemicals, and will allow the Agency to pursue necessary protective actions or mitigation if needed. We have committed, by 2012, to complete initial assessments and initiate needed actions on over 6,700 high production and moderate production volume chemicals. This builds on the work that EPA has done under the HPV challenge program, to obtain and assess screening level hazard and environmental fate information and use this new information reported under the TSCA inventory update regulations.

To meet these commitments, EPA is developing risk-based prioritizations for HPV chemicals based on hazard, exposure and risk screening characterizations. For the moderate production volume chemicals, we will rely on available data, Canada's work on chemical categorization and EPA's expertise in structural relationship analysis to prepare initial assessments. There is a down payment on these commitments. We have already posted hazard characterizations on 238 chemicals and in March, posted an initial set of risk-based prioritizations for 19 chemicals. These characterizations, which we make available on our website, provide important scientific information and analysis on hazards, exposure and risks, and position us to take any needed follow up actions. The 2012 commitment for completing the North American assessment work also sets up opportunities for cooperation with the European Union, given the timing of the REACH registration schedule, which extends from 2010 through 2018.

To foster cooperation, we have regular consultations with officials from the European Commission and OECD countries. It is vitally important to invest in this cooperation, to leverage work, avoid duplication and improve the protection of public health and the environment, both at home and abroad.

While we support the health and environmental goals of REACH, we believe that effective protection can be obtained through a more targeted and strategic approach to chemical assessment and management under our ChAMP efforts. In addition to the above commitments, where work is already underway, we are asking for feedback on potential enhancements to the ChAMP program, which combined with our 2012 commitments would provide the most comprehensive approach to dealing with chemicals that has ever been developed by the Environmental Protection Agency.

The first enhancement involves developing a program similar to the HPV challenge, but for inorganic HPV chemicals. The second enhancement under consideration would reset the TSCA inventory to better reflect the chemicals actually made, imported and used in the U.S. We have begun an extensive effort to invite input from a wide range of stakeholders.

I would like the Committee to know that the IRIS process that has been discussed today and the revisions to the process are managed by Dr. George Gray, the Assistant Administrator of EPA's Office of Research and Development. It is my understanding that ORD senior staff have already briefed the Committee on this effort.

Of course, the TSCA program does utilize the IRIS data base as a resource for reviewing chemicals, like our efforts under ChAMP. We work directly with ORD on a handful of assessments that are of particular relevance to us, like PFOS and PFOA. Again, while the IRIS data base provides my office with useful input, ORD is the lead for the overall process, and they would be best able to respond to questions on the recently announced process revisions.

I am pleased to be here to share with you the highlights of our chemicals work. We remain appreciative of the ongoing interest of this Committee in TSCA and our new efforts under ChAMP. I believe that TSCA provides EPA with the statutory tools necessary to protect public health and the environment, and the agency looks forward to continuing to work closely with members of this Committee, your staff and others from GAO.

Thank you.

[The prepared statement of Mr. Gulliford follows:]

Testimony of
Jim Gulliford
Assistant Administrator
Office of Prevention, Pesticides and Toxic Substances
U.S. Environmental Protection Agency
Before the
Committee on Environment and Public Works
U. S. Senate

April 29, 2008

I. Introduction

Good morning Madam Chair and members of the Committee, thank you for the invitation to speak with you today. It is my privilege to represent the U.S. Environmental Protection Agency during this oversight discussion on the Toxic Substances Control Act, or TSCA, as it is often called.

My office takes very seriously the responsibility to implement TSCA to protect both the American public and the environment from the adverse effects of chemicals. My testimony will focus on the tremendous progress that has been made in ensuring the safe manufacture and use of chemicals since the passage of TSCA more than three decades ago and highlight our efforts to strengthen chemicals management under the new Chemicals Assessment and Management Program (ChAMP).

II. Key Accomplishments

TSCA provides EPA with the authority needed to review and manage risks from new chemicals prior to introduction into commerce and to collect health and safety data as well as production, use, and exposure information on industrial chemicals in commerce. It gives EPA the authority to require testing on new or existing TSCA Inventory chemicals, to ban or take other risk mitigation actions on new or existing chemicals of concern, and to manage "legacy" chemicals such as PCBs, asbestos, and mercury. TSCA also provides EPA with the authority to oversee the import and export of chemicals and to enforce compliance with these rules and requirements.

With TSCA as the foundation, and recognizing the relationship of TSCA to, and the role of, other statutes which contribute to chemical safety, EPA is successfully utilizing a wide array of regulatory and voluntary approaches and tools to assist us in our mission to protect both human health and the environment.

For example, we use sophisticated modeling programs to assist both the Agency and industry in developing, reviewing, and manufacturing safer chemicals. We have incorporated broad pollution prevention approaches into our regulatory work and numerous voluntary programs, which have been highly successful and have considerably increased the speed at which we have been able to achieve environmental results. In order to make informed and transparent chemical management decisions, we have worked cooperatively with the regulated community, environmental stakeholders, our counterparts in other Federal Agencies, States, and tribes, and the public on a broad range of programs and activities. The Agency also works closely with the international community on chemical management issues to promote rigorous scientific standards and coordinate regulatory approaches to strengthen public health and environment protection for all.

Employing these various approaches and tools, EPA has successfully used TSCA over the years to review more than 47,000 new chemical submissions. We have taken regulatory actions – such as requirements for additional testing or restrictions -- on over 2,000 of these chemicals and an additional 1,746 new chemical submissions were withdrawn often in the face of Agency action. Since the passage of TSCA, more than 21,000 new chemicals have gone into production and have been added to the TSCA Inventory, for a total of 83,000 chemicals currently on the Inventory. In addition to the new chemicals, we have controlled or otherwise regulated 178 existing chemicals.

With TSCA as the regulatory backstop, we have collected health and safety data on 2,200 High Production Volume (HPV) chemicals, which cover more than 93% of organic chemical production volume EPA tracks on the TSCA Inventory.

Using Section 8 of TSCA, we have collected more than 50,000 health and environmental studies on existing chemicals. We have also received and assessed over 17,200 substantial risk submissions from the chemical industry since 1977. We have regularly collected updated production information on thousands of higher volume existing chemicals under the Inventory Update Rule, or IUR. In 2006, EPA expanded the information collected under the IUR to include inorganic chemicals, at greater than 25,000 lbs. per site, and exposure and use information on higher volume organic chemicals, above 300,000 lbs per site.

EPA has also successfully used TSCA to bring about the phase out of chemicals of concern such as penta- and octa-brominated diphenyl ethers, or BDEs, polybrominated biphenyls, and benzidene dyes, which are subject to Significant New Use Rule (SNUR) requirements for review by EPA prior to reintroduction into the marketplace to ensure that they could be safely used. EPA, during the Bush Administration, also took prompt regulatory action under TSCA by issuing SNURs on 271 perfluorooctyl sulfonates, or PFOS, derivatives EPA also successfully obtained commitments from national and international chemical manufacturers to reduce releases and work toward eliminating virtually all sources of exposure to perfluorooctanoic acid, or PFOA, PFOA precursors, and higher homologues. An indication of the EPA's success on PFOS and PFOA can be found in an August 2007 U.S. Centers for Disease Control report that showed significant reductions in human blood levels of PFOS and PFOA in 2003/2004 data when compared to 1999/2000 data. These data showed a reduction in blood concentrations of more than 25% over this period for PFOA and a 32% reduction for PFOS in human blood. The report concludes that these reductions most likely are related to the changes brought about by EPA efforts on these chemicals and other related efforts by government and industry.

EPA also used TSCA as the foundation for addressing nanoscale materials under its jurisdiction. This past January, EPA announced the Nanoscale Materials Stewardship Program. This program will allow us to quickly assemble information EPA needs to scientifically assess – and where appropriate – take risk

management actions on nanoscale materials consistent with the "Principles for Nanotechnology Environmental, Health and Safety Oversight", released on November 8, 2007, we are encouraging active industry participation in this program to strengthen our scientific understanding in this exciting new arena. While implementing the program, EPA will continue to consider, as appropriate, the timing and use of all of its authority under TSCA for nanoscale materials.

Overall, I believe that TSCA provides broad authority for the Agency to adequately control new and existing chemicals and to address emerging chemical issues as they arise. The Agency's successful efforts to address PFOS, PFOA, and BDEs, and the introduction of nanoscale materials, provide clear examples demonstrating this point.

III. Chemical Assessment and Management Program

This past August, the countries of North America came together to announce a strategic approach under the Security and Prosperity Partnership, or SPP. At the SPP Leaders' Summit in Quebec, President Bush, Canadian Prime Minister Stephen Harper, and Mexican President Felipe Calderon committed our three countries to work together to accelerate and strengthen the management of chemicals in North America while preserving national sovereignty.

As part of this effort, the United States committed, by 2012, to complete initial assessments and take needed actions on 6,750 chemicals produced above 25,000 pounds-per-year in the U.S. This commitment, which we refer to as the Chemical Assessment and Management Program, or ChAMP, includes both high-production volume chemicals, those produced at or above one million pounds per year, and moderate volume chemicals, produced between 25,000 and a million pounds per year. The ability to make this commitment represents the culmination of the work that EPA did under the HPV Challenge Program to obtain screening level hazard and environmental fate information and under the Inventory Update Rule to obtain exposure and use information, which will now inform risk prioritization decisions on HPV chemicals. For the moderate volume chemicals, we will rely on available data, Canada's work on

chemical categorization, and EPA's expertise in Structure Activity Relationship analysis to prepare initial assessments. The U.S. and Canada have also agreed to share scientific information, technical understanding, research strategies and best practices, and to collaborate when possible on risk assessment and management efforts.

I believe that this collaborative effort to collect and share information on thousands of high and moderate production volume chemicals will foster efficiencies that through our shared efforts will enable us to act more quickly, effectively, and cost-efficiently on a greater number of chemicals. Our efforts under ChAMP will result in greater public health and environmental protection in the U.S. and will also help ensure a more consistent, efficient, and better integrated approach to chemicals assessment and management throughout North America. The 2012 commitment for completing the North American assessment work will also allow the U.S. and the EU to share information on our chemicals work given the timing of the European Union's Registration, Evaluation, Authorization and Restriction of Chemical substances, or REACH, registration schedule, which extends from 2010 to 2018.

In order to meet our SPP commitments under ChAMP, EPA is developing risk-based prioritizations for HPV chemicals, based on hazard, exposure and risk-screening characterizations, and considering other relevant information such as biomonitoring. We have posted hazard characterizations on 238 chemicals and, in March, posted an initial set of risk-based prioritizations on 19 chemicals. These characterizations provide important scientific information and analysis on hazards, exposure, and risks, thereby positioning the Agency to take any needed follow-up actions.

Recognizing that many chemicals are in commerce internationally and that countries and regions beyond North America have on-going chemical assessment and management efforts, we have on-going consultations with European Commission officials dealing with REACH, and with OECD countries, including France, the UK, New Zealand, Australia, Japan, and Korea. I believe that it is vitally important to invest in this coordination, to the greatest extent possible, so that our efforts and the international efforts to assess

and manage chemicals are utilized to leverage work, avoid duplication, and improve the protection of public health and the environment, both at home and abroad.

The members of this Committee may also be aware that last month, EPA Administrator Stephen Johnson asked me and my Office to engage all our stakeholders on two possible enhancements to our ChAMP work on existing chemicals under TSCA. The first involves possibly developing a program similar to the HPV Challenge for "inorganic" HPV chemicals, an effort that would provide the Agency, industry, and the public with a more complete picture of the hazards and risks of all HPV chemicals presently in U.S. commerce. The second possible enhancement concerns how best to reset the TSCA Inventory to better reflect the chemicals actually made and used in the U.S. As I highlighted earlier, the TSCA Inventory now lists more than 83,000 chemicals – a significant number of which are likely no longer being produced or imported. We believe it is time to consider options for making the Inventory a more useful list for all of us – EPA, industry, and the public – and one that reflects the chemicals actually in commerce.

As we begin these efforts to realize an enhanced ChAMP program, we have begun an extensive effort to invite input from a wide range of stakeholders, including meetings and "webinars" with companies, trade associations, the NGO community, States and Tribes, others in the Federal Government, and the public, including a "town hall" type meeting on May 2nd here in Washington. We appreciate the opportunity to hear from Congress on these enhancements as well.

We recognize that there are a range of issues that we will need to work through, which is why we are seeking input from others, but it is our hope to conclude discussions on these enhancements by mid-June, report back to the Administrator this summer, and begin implementing the new efforts for both inorganic HPV chemicals and the TSCA Inventory reset by the end of the summer.

IV. Conclusion

As I conclude my remarks, I would like to reiterate a point I made in 2006 when I testified on this subject. While we remain appreciative of the on-going interest of this Committee in TSCA and our new

efforts under ChAMP, I would also like to reiterate my statement at the beginning of my testimony; I believe that TSCA provides EPA with the statutory tools necessary to protect public health and environment. We are committed to using sound science to make risk-based decisions and take needed regulatory actions that are complemented, where appropriate, with effective collaborative environmental stewardship programs. We are also committed to working with governments around the world on chemical assessment and management programs.

The Agency looks forward to continuing to work closely with members of this Committee and your staffs. There are many dedicated engineers, chemists, biologists, toxicologists, economists, statisticians, attorneys and other civil servants who work directly on TSCA issues at EPA. I have been most impressed with their scientific and technical capabilities during my time as the Assistant Administrator for OPPTS. They have worked extremely hard over the years to effectively implement the many TSCA accomplishments I highlighted today and I am sure you share with me an appreciation for their efforts.

Again, I thank you for the opportunity to be here today and to provide you with this information. I am happy to answer any questions you may have today or any written questions in the future.

Senator BOXER. Mr. Stephenson, thank you.

STATEMENT OF JOHN B. STEPHENSON, DIRECTOR, NATURAL RESOURCES AND ENVIRONMENT, U.S. GOVERNMENT ACCOUNTABILITY OFFICE

Mr. STEPHENSON. Thank you, Madam Chairman, members of the Committee.

GAO has issued several reports on EPA's implementation of TSCA and EPA's voluntary programs to control dangerous chemicals. We have concluded in this work that TSCA is outdated, cumbersome and difficult to use in controlling the more than 80,000 chemicals currently in the inventory.

Since TSCA was enacted in 1976, EPA has used its authority to require chemical industry testing for fewer than 200 chemicals, that is in 30 years, and has issued regulations to limit or ban the production of only 5 chemicals or groups of chemicals in that same time. Voluntary programs provide EPA useful information, but they don't negate the need to overhaul TSCA.

In comparing the U.S. approach for controlling dangerous chemicals under TSCA to the European Union approach under the REACH program, we note that TSCA places the burden of proof on EPA to demonstrate that the chemical poses a risk to human health before it can regulate its production or use, whereas in Europe, REACH generally places the burden of proof on the chemical industry to ensure that chemicals do not pose such risks or that measures will be taken for handling chemicals safely.

My written statement includes additional information from the toxic chemical control reports we have issued over the past couple of years, but I want to focus my comments today on our new report concerning EPA's Integrated Risk Information System, or IRIS, a data base that contains EPA's scientific position on potential health effects of exposure to more than 540 toxic chemicals. IRIS is a critical component of EPA's capacity to support scientifically sound environmental decisions, policies and regulations.

In summary, we found that the IRIS data base is at serious risk of becoming obsolete, because the EPA has not been able to routinely complete timely, credible assessments or decrease its backlog of 70 ongoing assessments. Our report recognizes steps EPA has taken to improve IRIS since 2000, such as increasing funding and centralizing staff, but points out that these efforts have been thwarted by new OMB-required interagency reviews, the growing complexity and scope of chemical assessments, EPA decisions to delay assessments to wait for new research or additional uncertainty analysis on a given chemical and the compounding effects of delays.

While EPA has prepared over 32 toxic chemical assessments for external review in the past two fiscal years, only four have been finalized. Comments by the National Academies on EPA's assessment of trichloroethlyene or TCE highlight the problem. In 1998, EPA initiated a risk assessment of TCE, a degreasing agent used widely by the Department of Defense and others. EPA's Science Advisory Board approved the draft risk assessment for public comment in 2001. DOD and others raised questions about the assessment, which led to a National Academies review. The Academies

specifically noted in its 2006 report that the risks of TCE were substantial and that additional studies were not necessary to finalize an assessment needed to protect public health.

Nonetheless, after more than 10 years, TCE is back at the draft development stage. To get EPA moving, Senators Clinton, Boxer, Lautenberg, Kerry and Dole, spurred by TCE contamination in drinking water at Camp LeJeune, introduced a bill last August that would require EPA to complete its risk assessment and issue a drinking water standard in 18 months.

Our report contains eight specific recommendations to EPA for streamlining the IRIS program, improving the transparency and credibility of its assessments and ensuring that EPA has the requisite independence to achieve these goals. EPA agreed to consider our recommendations in its February comments on our draft report. EPA released its revised IRIS assessments process after the report on April 10th.

It is an understatement to say that we are disappointed in EPA's response. The revised IRIS process is not improved and is in many respects worse than the draft we reviewed. For example, transparency is a cornerstone of sound science. And the draft IRIS process we reviewed would have made comments from other Federal agencies part of the public record.

However, EPA's new process expressly defines such comments as deliberative, excluding them from the public record. This new process will exacerbate the problems we identified in our report and sought to address with our recommendations, all of which were aimed at preserving the viability of this critical data base, which is integral to the EPA's mission of protecting the public and the environment from exposure to toxic chemicals.

In light of the importance of the IRIS program, we believe that Congress should consider directing EPA to suspend implementation of its new IRIS process and develop one that is responsive to our recommendations for a streamlined, fully, not selectively transparent process aimed at improving the timeliness and credibility of IRIS assessments. EPA should also seek congressional and public input before finalizing IRIS.

Madam Chairman, that concludes the summary of my statement.

[The prepared statement of Mr. Stephenson follows:]

United States Government Accountability Office

GAO

Testimony
Before the Committee on Environment and Public Works, U.S. Senate

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TOXIC CHEMICALS

EPA's New Assessment Process Will Increase Challenges EPA Faces in Evaluating and Regulating Chemicals

Statement of John B. Stephenson, Director
Natural Resources and Environment

GAO-08-743T

GAO

Highlights

Highlights of GAO-08-774T, a testimony before the Committee on Environment and Public Works, U.S. Senate

Why GAO Did This Study

The Environmental Protection Agency's (EPA) mission includes evaluating and regulating toxic chemicals. EPA's Integrated Risk Information System (IRIS) program is a chemical evaluation program that is a critical component of EPA's capacity to support scientifically sound environmental regulations and policies. The IRIS database contains EPA's scientific position on the potential human health effects of exposure to more than 540 chemicals.

This testimony highlights GAO's work on toxic substances, focusing on (1) its March 2008 report, Chemical Assessments: Low Productivity and New Interagency Review Process Limit the Usefulness and Credibility of EPA's Integrated Risk Information System, and (2) key changes to the IRIS assessment process EPA included in its revised IRIS assessment process released on April 10, 2008. It also highlights the findings of two GAO reports on EPA's regulation of toxic chemicals. For the IRIS report, GAO analyzed EPA data and interviewed officials at relevant agencies, including the Office of Management and Budget (OMB). For this testimony, GAO supplemented the IRIS report with a review of EPA's revised IRIS assessment process announced earlier this month.

Given the importance of the IRIS program to EPA's ability to protect public health and the environment, Congress should consider requiring EPA to suspend its new process and develop one that is responsive to GAO's recommendations.

To view the full product, including the scope and methodology, click on GAO-08-774T. For more information, contact John B. Stephenson at (202) 512-3841 or stephensonj@gao.gov.

April 29, 2008

TOXIC CHEMICALS

EPA's New Assessment Process Will Increase Challenges EPA Faces in Evaluating and Regulating Chemicals

What GAO Found

The IRIS database is at serious risk of becoming obsolete because EPA has not been able to routinely complete timely, credible assessments or decrease its backlog of 70 ongoing assessments—a total of 4 were completed in fiscal years 2006 and 2007. In addition, recent assessment process changes, as well as other changes EPA was considering at the time of GAO's review, further reduce the timeliness and credibility of IRIS assessments.

- Although EPA has taken steps to improve the IRIS program since 2000 and has developed a number of draft assessments for external review, its efforts to finalize assessments have been thwarted by a combination of factors, including two new OMB-required reviews of IRIS assessments by OMB and other federal agencies; EPA management decisions, such as delaying some assessments to await new research; and the compounding effect of delays—even one delay can have a domino effect, requiring the process to essentially be repeated to incorporate changing science and methods.
- The OMB/interagency reviews of draft assessments involve other federal agencies in EPA's IRIS assessment process in a manner that limits the credibility of IRIS assessments and hinders EPA's ability to manage them. For example, the OMB/interagency reviews lack transparency, and OMB required EPA to terminate five assessments EPA had initiated to help it implement the Clean Air Act.
- The changes to the IRIS assessment process that EPA was considering, but had not yet issued at the time of GAO's review, would have added to the already unacceptable level of delays in completing IRIS assessments and further limited the credibility of the assessments.

On April 10, 2008, EPA issued a revised IRIS assessment process, effective immediately. In its February 2008 comments on GAO's draft report, EPA said it would consider the report's recommendations, which were aimed at streamlining the process and better ensuring that EPA has the ability to develop transparent, credible assessments. However, EPA's new process is largely the same as the draft GAO evaluated, and some key changes also are likely to further exacerbate the productivity and credibility concerns GAO identified. For example, while the draft process would have made comments on IRIS assessments from other federal agencies part of the public record, EPA's new process expressly defines such comments as "deliberative" and excludes them from the public record. GAO continues to believe it is critical that input from all parties—particularly agencies that may be affected by the outcome of IRIS assessments—be publicly available. As recommended in GAO's March 2008 report, to effectively maintain IRIS, EPA must, among other things, streamline its lengthy assessment process and adopt transparency practices that provide assurance that IRIS assessments are appropriately based on the best available science and that they are not inappropriately biased by policy considerations. Since EPA's new process is not responsive to GAO's recommendations, the viability of this critical database has been further jeopardized.

Madam Chairman and Members of the Committee:

I am pleased to be here today to discuss issues associated with the Environmental Protection Agency's (EPA) evaluation and regulation of toxic chemicals. Over the past few years, GAO has issued a number of reports on this topic. Today I will focus primarily on our most recent report in this area that examined EPA's Integrated Risk Information System (IRIS)—one of the most significant tools that EPA has developed to effectively support its mission of protecting people and the environment from harmful chemical exposures. IRIS contains EPA's scientific position on the potential human health effects that may result from exposure to more than 540 chemicals in the environment and is a critical component of EPA's capacity to support scientifically sound environmental decisions, policies, and regulations. It is also relied upon by state and local environmental programs and some international regulatory bodies for managing their environmental protection programs.

The toxicity assessments in the IRIS database fulfill the first two critical steps of the risk assessment process—providing hazard identification and quantitative dose-response assessments. IRIS information can then be used with the results of exposure assessments (typically conducted by EPA's program or regional offices) to provide an overall characterization of the public health risks for a given chemical in a given situation. The development of health risk assessments is thus directly dependent on the development of toxicity assessments such as those developed in the IRIS program. With risk assessment information, decision makers can make informed risk management decisions on how to protect public health, reflecting other important data and considerations, such as the costs and benefits of mitigating identified risks, the technological feasibility of managing risks, and the concerns of various stakeholders. Examples of risk management decisions include deciding how much of a chemical a company may discharge into a river, determining the extent to which a hazardous waste site must be cleaned up, and setting allowable levels of contamination in drinking water. Thus, as EPA has recognized, although IRIS assessments are not regulatory in nature, the quantitative IRIS values may influence many risk management decisions and serve as a

basis for regulatory consideration. However, EPA's productivity in finalizing IRIS assessments is poor, and EPA has a significant backlog of incomplete IRIS assessments and a growing number of outdated assessments. Importantly, EPA has not been able to complete assessments of key chemicals of concern to public health, including dioxin, formaldehyde, trichloroethylene (TCE), naphthalene, and tetrachloroethylene (perc) (see app. I).

In the last several years, GAO issued a number of reports on EPA's toxics programs, highlighting program shortcomings and recommending management improvements. My testimony today addresses (1) the highlights of our March 2008 report, *Chemical Assessments: Low Productivity and New Interagency Review Process Limit the Usefulness and Credibility of EPA's Integrated Risk Information System*,[1] being released today, and (2) key changes to the IRIS assessment process that EPA included in its revised process released on April 10, 2008. We are also providing information on two of our prior reports on EPA's regulation of toxic chemicals (see app. II).[2] For our March 2008 report, we examined the outcome of steps EPA has taken to ensure that IRIS contains current, credible chemical risk information; to address the backlog of ongoing assessments; and to respond to new requirements from the Office of Management and Budget (OMB). We also examined the potential effects of planned changes to the IRIS assessment process on EPA's ability to ensure that IRIS provides current, credible risk information. In conducting our work, we obtained and analyzed information on EPA's productivity and the resources provided to the program for fiscal years 2000 through 2007, user needs, and EPA's assessment completion goals. We also interviewed EPA's National Center for Environmental Assessment officials who manage the IRIS assessment program; officials from other EPA program offices and federal science and health agencies involved in the IRIS assessment process; and officials from the Department of Defense, the Department of Energy (DOE), the National Aeronautics and

[1]GAO-08-440 (Washington, D.C.: Mar. 7, 2008).
[2]GAO, *Chemical Regulation: Options Exist to Improve EPA's Ability to Assess Health Risks and Manage Its Chemical Review Program*, GAO-05-458 (Washington, D.C.: June 13, 2005); and GAO, *Chemical Regulation: Approaches in the United States, Canada, and the European Union*, GAO-06-217R (Washington, D.C.: Nov. 4, 2005).

Space Administration (NASA), and OMB. For this testimony, we supplemented our report with an analysis of the IRIS assessment process that EPA released on April 10, 2008. We conducted this work from April 16 to April 29, 2008, in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Background

IRIS was created in 1985 to help EPA develop consensus opinions within the agency about the health effects of chronic exposure to chemicals. Its importance has increased over time as EPA program offices and the states have increasingly relied on IRIS information in making environmental protection decisions. Currently, the IRIS database contains assessments of more than 540 chemicals. According to EPA, national and international users access the IRIS database approximately 9 million times a year. EPA's Assistant Administrator for the Office of Research and Development has described IRIS as the premier national and international source for qualitative and quantitative chemical risk information; other federal agencies have noted that IRIS data are widely accepted by all levels of government across the country for application of public health policy, providing benefits such as uniform, standardized methods for toxicology testing and risk assessment, as well as uniform toxicity values. Similarly, a private-sector risk assessment expert has stated that the IRIS database has become the most important source of regulatory toxicity values for use across EPA's programs and is also widely used across state programs and internationally.

A typical IRIS assessment contains a qualitative hazard identification description and quantitative dose-response assessments. Historically and currently, the focus of IRIS toxicity assessments has been on the potential health effects of long-term (chronic) exposure to chemicals. According to OMB, EPA is the only federal agency that develops

qualitative and quantitative assessments of both cancer and noncancer risks of exposure to chemicals, and EPA does so largely under the IRIS program. Other federal agencies develop quantitative estimates of noncancer effects or qualitative cancer assessments of exposure to chemicals in the environment. While these latter assessments provide information on the effects of long-term exposures to chemicals, they provide only qualitative assessments of cancer risks (known human carcinogen, likely human carcinogen, etc.) and not quantitative estimates of cancer potency, which are required to conduct quantitative risk assessments.

EPA's IRIS assessment process has undergone a number of formal and informal changes during the past several years. While the process used to develop IRIS chemical assessments includes numerous individual steps or activities, major assessment steps include (1) a review of the scientific literature; (2) preparation of a draft IRIS assessment; (3) internal EPA reviews of draft assessments; (4) two OMB/interagency reviews, managed by OMB, that provide input from OMB as well as from other federal agencies, including those that may be affected by the IRIS assessments if they lead to regulatory or other actions; (5) an independent peer review conducted by a panel of experts; and (6) the completion of a final assessment that is posted to the IRIS Web site.

Findings and Recommendations from Our March 2008 Report on the Productivity and Credibility of EPA's Integrated Risk Information System

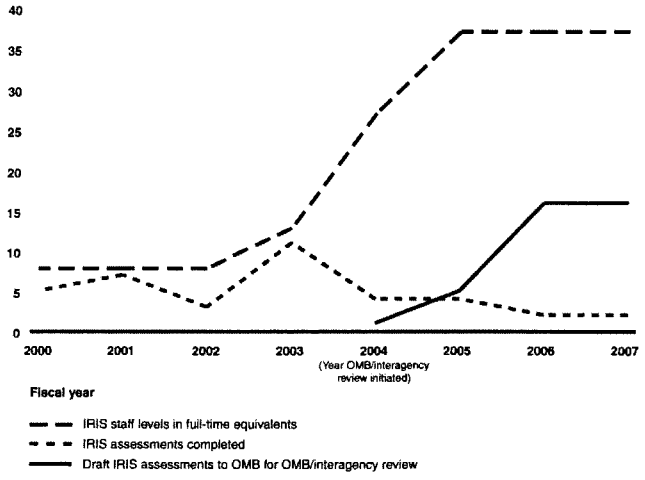
The IRIS database is at serious risk of becoming obsolete because the agency has not been able to routinely complete timely, credible assessments or decrease a backlog of 70 ongoing assessments. Specifically, although EPA has taken important steps to improve the IRIS program and productivity since 2000 and has developed a number of draft assessments for external review, its efforts to finalize the assessments have been thwarted by a combination of factors including the imposition of external requirements, the growing complexity and scope of risk assessments, and certain EPA management decisions. In addition, the changes to the IRIS assessment process that EPA was considering at the time of our review would have added to the already unacceptable level

of delays in completing IRIS assessments and further limited the credibility of the assessments.

EPA's Efforts to Improve the IRIS Assessment Program Have Not Produced the Desired Results

EPA has taken a number of steps to help ensure that IRIS contains current, credible chemical risk information; to address its backlog of ongoing assessments; and to respond to new OMB requirements. However, to date, these changes—including increasing funding, centralizing staff conducting assessments, and revising the assessment process—have not enabled EPA to routinely complete credible IRIS assessments or decrease the backlog. That is, although EPA sent 32 draft assessments for external review in fiscal years 2006 and 2007, the agency finalized only 4 IRIS assessments during this time (see fig. 1).

Figure 1: Number of Completed IRIS Assessments, Draft Assessments to OMB, and IRIS Staff in Full-Time Equivalents, Fiscal Years 2000-2007



Source: GAO analysis of EPA data.

Several key factors have contributed to EPA's inability to achieve a level of productivity that is needed to sustain the IRIS program and database: new OMB-required reviews of IRIS assessments by OMB and other federal agencies; the growing complexity and scope of risk assessments; certain EPA management decisions and issues, including delaying completion of some assessments to await new research or to develop enhanced analyses of uncertainty in the assessments; and the compounding effect of delays. Regarding the last factor, even a single delay in the assessment process can lead to the need to essentially repeat the assessment process to take into account changes in science and methodologies.

A variety of delays have impacted the majority of the 70 assessments being conducted as of December 2007—48 had been in process for more than 5 years, and 12 of those for more than 9 years. These time frames are problematic because of the substantial rework such cases often require to take into account changing science and methodologies before they can be completed. Further, because EPA staff time continues to be dedicated to completing these assessments, EPA's ability to both keep the more than 540 existing assessments up to date and initiate new assessments is limited. Importantly, EPA program offices and state and local entities have requested assessments of hundreds of chemicals not yet in IRIS, and EPA data as of 2003 indicated that the assessments of 287 chemicals in the database may be outdated—that is, new information could change the risk estimates currently in IRIS or enable EPA to develop additional risk estimates for chemicals in the database (for example, developing a cancer potency estimate for assessments with only noncancer estimates). In addition, because EPA's 2003 data are now more than 4 years old, it is likely that more assessments may be outdated now.

One of the factors that has contributed to EPA's inability to complete assessments in a timely manner—the new OMB-directed OMB/interagency review process—also limits the credibility of the assessments because it lacks transparency. Specifically, neither the comments nor the changes EPA makes to the scientific IRIS assessments in response to the comments made by OMB and other federal agencies, including those whose

workload and resource levels could be affected by the assessments, are disclosed. In addition, the OMB/interagency reviews have hindered EPA's ability to independently manage its IRIS assessments. For example, without communicating its rationale for doing so, OMB directed EPA to terminate five IRIS assessments that for the first time addressed acute, rather than chronic exposure—even though EPA initiated this type of assessment to help it implement the Clean Air Act.

The Expansion of Agencies' Roles in IRIS Assessments That EPA Was Considering at the Time of Our Review Would Have Caused Further Delays and Limited the Assessments' Credibility

For our March 2008 report, we reviewed the additional assessment process changes EPA was planning and concluded that they would likely exacerbate delays in completing IRIS assessments and further affect their credibility. Specifically, despite the OMB/interagency review process that OMB required EPA to incorporate into the IRIS assessment process in 2005, certain federal agencies continued to believe they should have greater and more formal roles in EPA's development of IRIS assessments. Consequently, EPA had been working for several years to establish a formal IRIS assessment process that would further expand the role of federal agencies in the process—including agencies such as DOD, which could be affected by the outcome of IRIS assessments. For example, some of these agencies and their contractors could face increased cleanup costs and other legal liabilities if EPA issued an IRIS assessment for a chemical that resulted in a decision to regulate the chemical to protect the public. In addition, the agencies could be required to, for example, redesign systems and processes to eliminate hazardous materials; develop material substitutes; and improve personal protective clothing, equipment, and procedures. Under the changes that EPA was planning at the time of our review, these potentially affected agencies would have the opportunity to be involved, or provide some form of input, at almost every step of EPA's IRIS assessment process. Most significantly, the changes would have provided federal agencies, including those facing potential regulatory liability, with several opportunities during the IRIS assessment process to subject particular chemicals of interest to additional process steps. These additional process steps, which would have lengthened assessment times considerably, include

- giving federal agencies and the public 45 days to identify additional information on a chemical for EPA's consideration in its assessment or to correct any errors on an additional assessment draft that would provide qualitative information;[3]
- giving potentially affected federal agencies 30 days to review the public comments EPA received and initiate a meeting with EPA if they want to discuss a particular set of comments;
- allowing potentially affected federal agencies to have assessments suspended for up to 18 months to fill a data gap or eliminate an uncertainty factor that EPA plans to use in its assessment; and
- allowing other federal agencies to weigh in on (1) the level of independent peer review that would be sought (that is, whether the peer reviews would be conducted by EPA Science Advisory Board panels, National Academies' panels, or panels organized by an EPA contractor); (2) the areas of scientific expertise needed on the panel; and (3) the scope of the peer reviews and the specific issues they would address.

EPA estimated that assessments that undergo these additional process steps would take up to 6 years to complete. While it is important to ensure that assessments consider the best science, EPA has acknowledged that waiting for new data can result in substantial harm to human health, safety, and the environment. Further, although coordination with other federal agencies about IRIS assessments could enhance their quality,[4] increasing the role of agencies that may be affected by IRIS assessments in the process itself reduces the credibility of the assessments if that expanded role is not transparent. In this regard, while EPA's proposed changes would have allowed for including federal agencies' comments in the public record, the implementation of this proposal was delayed for a year, in part, because of OMB's view that agencies' comments about IRIS

[3]This represents an additional review of a new draft product and comment period that had not existed previously.

[4]We recommended in our 2006 report on human health risk assessment that EPA consistently involve stakeholders as appropriate to the risk assessment. We made this recommendation in the context of improving the overall quality, consistency, and transparency of risk assessments. GAO, *Human Health Risk Assessment: EPA Has Taken Steps to Strengthen Its Process, but Improvements Needed in Planning, Data Development, and Training*, GAO-06-595 (Washington, D.C.: May 31, 2006).

assessments represent internal executive branch communications that may not be made public—a view that is inconsistent with the principle of sound science, which relies on, among other things, transparency.

Recommendations Made in Our March 2008 Report

To address the productivity and credibility issues we identified, we recommended that the EPA Administrator require the Office of Research and Development to re-evaluate its draft proposed changes to the IRIS assessment process in light of the issues raised in our report and ensure that any revised process, among other things, clearly defines and documents an IRIS assessment process that will enable the agency to develop the timely chemical risk information it needs to effectively conduct its mission. One of our recommendations—that EPA provide at least 2 years' notice of IRIS assessments that are planned—would, among other things, provide an efficient alternative to suspending assessments while waiting for new research because interested parties would have the opportunity to conduct research before assessments are started.

In addition, we recommended that the EPA Administrator take steps to better ensure that EPA has the ability to develop transparent, credible IRIS assessments—an ability that relies in large part on EPA's independence in conducting these important assessments. Actions that are key to this ability include ensuring that EPA can (1) determine the types of assessments it needs to support EPA programs and (2) define the appropriate role of external federal agencies in EPA's IRIS assessment process and manage an interagency review process in a manner that enhances the quality, transparency, timeliness, and credibility of IRIS assessments. In its February 21, 2008, letter providing comments on our draft report, EPA said it would consider each of our recommendations in light of the new IRIS process the agency was developing.

Key Changes to the IRIS Assessment Process That EPA Implemented in April 2008

On April 10, 2008, EPA issued a revised IRIS assessment process, effective immediately (see app. III for a flow chart of the process). Overall, EPA's revised process is not responsive to the recommendations made in our March 2008 report. While the revised process is largely the same as the draft proposed process we evaluated in our March 2008 report, there are several key differences that are likely to further exacerbate the productivity and credibility issues we identified in our report. These changes are as follows.

- While the draft process we reviewed provided that comments on IRIS assessments from OMB and other federal agencies would be part of the public record, under the recently implemented process, comments from federal agencies are expressly defined as "deliberative" and will not be included in the public record. (Making these comments public would have been a change from the OMB/interagency review process that has been in place since 2004.) Given the importance and sensitivity of IRIS assessments, we believe it is critical that input from all parties, particularly agencies that may be affected by the outcome of IRIS assessments, be publicly available. Thus, under EPA's new process, input from some IRIS assessment reviewers—representatives of federal agencies, including those facing potential regulatory liability, and private stakeholders associated with these agencies—will continue to receive less public scrutiny than all other comments.

- The newly implemented IRIS assessment process broadens EPA's characterization of IRIS assessments from "the Agency's scientific positions on human health effects that may result from exposure to environmental contaminants" to "the Agency's science and science policy positions" on such effects. As we highlighted in our report, under the National Academies' risk assessment and risk management paradigm, policy considerations are relevant in

the risk management phase—which occurs *after* the risk assessment phase that encompasses IRIS assessments. EPA's new, broader characterization of IRIS raises concerns about the agency's intent to ensure that scientific assessments are appropriately based on the best available science and that they are not inappropriately impacted by policy issues and considerations.

- The new process includes several revisions to the time frames associated with various process steps. Most notably, while EPA has estimated that under the new process assessments may take up to 6 years to complete, the estimated time frames do not factor in the time needed for peer reviews conducted by the National Academies, which can take 2 years to plan and complete.[5] EPA typically uses reviews by the National Academies for highly controversial chemicals or complex assessments. Therefore, assessments reviewed by the National Academies are likely to take at least 8 years to complete. However, as discussed in our report, when assessments take longer than 2 years, they can become subject to substantial delays stemming from the need to redo key analyses to take into account changing science and assessment methodologies. As a result, we concluded that it was critical that EPA streamline its process to routinely support timely completion of assessments and avoid being caught in an endless cycle of delays. Further, EPA's lengthy assessment time frames must be considered in light of OMB's view that health assessment values in IRIS are out of date if they are more than 10 years old and if new scientific information exists that could change the health assessment values. EPA's new process institutionalizes time frames that could essentially require the agency to start assessment updates as soon as 2 years after assessments are finalized in order to keep the IRIS database current. Such time frames are not consistent with our recommendation that EPA clearly define and document a streamlined IRIS process that can be conducted within time frames that minimize the need for wasteful rework. Further, the agency

[5]It is not clear whether the time frames exclude reviews conducted by EPA's Science Advisory Board, which can also add considerably more time than the most basic level of peer review used by the IRIS program—panels organized by an EPA contractor.

would need a significant increase in resources to support such an assessment cycle.

In addition, EPA had previously emphasized that, in suspending assessments to allow agencies to fill in data gaps, it would allow no more than 18 months to complete the studies and have them peer reviewed. However, under the new process, EPA states that it *generally* will allow no more than 18 months to complete the studies and have them peer reviewed. As we concluded in our report, we believe the ability to suspend assessments for up to 18 months would add to the already unacceptable level of delays in completing IRIS assessments. Further, we and several agency officials with whom we spoke believe that the time needed to plan, conduct, and complete research that would address significant data gaps, and have it peer reviewed, would likely exceed 18 months. Therefore, the less rigid time frame EPA included in its new process could result in additional delays.

- The new process expands the scope of one of the additional steps that initially was to apply only to chemicals of particular interest to federal agencies.[6] Specifically, under the draft process we reviewed, EPA would have provided an additional review and comment opportunity for federal agencies and the public for what EPA officials said would be a small group of chemicals. However, under EPA's new process, this additional step has been added to the assessment process for all chemicals and, therefore, will add time to the already lengthy assessments of all chemicals.

- Finally, EPA and OMB had planned for EPA to release a draft revised IRIS assessment process to the public, hold a public meeting to discuss EPA's

[6]The new IRIS assessment process refers to such chemicals as "mission critical." A mission-critical chemical is one that is an integral component to the successful and safe conduct of an agency's mission in any or all phases of its operations. Impacts on the use of mission-critical chemicals include cessation or degradation of the conduct of the mission and/or unacceptable resource constraints.

proposed changes, and seek and incorporate public input before finalizing the process. For example, in its letter commenting on our draft report, OMB emphasized that EPA had not completed the development of the IRIS assessment process, adding: "Indeed, the process will not be complete until EPA circulates its draft to the public for comments and then releases a final product that is responsive to those comments." However, as stated above, EPA released its new assessment process without obtaining public input and made it effective immediately.

Conclusions

The new IRIS assessment process that EPA implemented in April 2008 will not allow the agency to routinely and timely complete credible assessments. In fact, it will exacerbate the problems we identified in our March 2008 report and sought to address with our recommendations—all of which were aimed at preserving the viability of this critical database, which is integral to EPA's mission of protecting the public and the environment from exposure to toxic chemicals. Specifically, under the new process, assessment time frames will be significantly lengthened, and the lack of transparency will further limit the credibility of the assessments because input from OMB and other agencies at all stages of the IRIS assessment process is now expressly defined as deliberative and therefore not subject to public disclosure. To effectively maintain IRIS, EPA must streamline its lengthy assessment process and adopt transparency practices that provide assurance that IRIS assessments are appropriately based on the best available science and that they are not inappropriately biased by policy issues and considerations. Federal agencies may appropriately participate in policy dialogues through the rule-making process and other interagency working groups, which are risk management activities that should occur after the risk assessment process that encompasses IRIS assessments. Finally, suspending assessments is inefficient; alternatively, with longer-term planning, EPA could provide agencies and the public with more advance notice of assessments, enabling them to complete relevant research before IRIS assessments are started.

Matter for Congressional Consideration

In light of the importance of the IRIS program to EPA's ability to protect the public health and the environment, the Congress should consider requiring EPA to suspend implementation of its new IRIS assessment process and develop a process that is responsive to our recommendations for a streamlined process that is transparent and otherwise responsive to our recommendations aimed at improving the timeliness and credibility of IRIS assessments. In addition, the Congress should consider requiring EPA to obtain and be responsive to input from the Congress and the public before finalizing a revised IRIS assessment process.

Madam Chairman, this concludes my prepared statement. I would be happy to respond to any questions that you or other Members of the Committee may have at this time.

Contacts and Acknowledgments

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Appendix I: Examples of Key IRIS Assessments That Have Been Delayed

Some key IRIS assessments have been in progress for a number of years, in part because of delays stemming from one or more of the key factors we identified that have hindered EPA's productivity.[7] Examples include the following:

Naphthalene. EPA started the IRIS assessment of cancer risks stemming from the inhalation of naphthalene in 2002. Naphthalene is used in jet fuel and in the production of widely used commercial products such as moth balls, dyes, insecticides, and plasticizers. According to a presentation delivered at the 2007 annual meeting of the Society for Risk Analysis by an Army Corps of Engineers toxicologist,[8] "The changing naphthalene regulatory environment includes a draft EPA risk assessment that if/when finalized, will change naphthalene's status from 'possible' to 'likely' human carcinogen."[9] Thus, according to this presentation, one potential impact of this IRIS assessment on DOD is that DOD would need to provide many employees exposed to naphthalene with equipment measuring their exposure to the chemical. In addition, because many military bases are contaminated with naphthalene, a component of jet fuel (approximately 1 percent to 3 percent) used by all DOD services, DOD could face extensive cleanup costs. By 2004, 2 years after starting the assessment, EPA had drafted a chemical assessment that had completed internal peer reviews and was about to be sent to an external peer review committee. Once it returned from external review, the next step, at that time, would have been a formal review by EPA's IRIS Agency Review Committee. If approved,

[7]The factors we identified that have hindered EPA's efforts to improve productivity are the OMB/interagency review process managed by OMB, the growing complexity and scope of risk assessments, certain management decisions and issues regarding the IRIS program, congressional action that has delayed some assessments with potentially significant economic effects, and the compounding effect of delays.

[8]Presentations at the Society for Risk Analysis meeting reflect the views of the authors and "do not necessarily reflect the views of any other organization or agency."

[9]Using its 1996 Proposed Guidelines for Carcinogen Risk Assessment, EPA concluded in the 1998 IRIS assessment of naphthalene that its human carcinogenic potential could not be determined at that time, but noted that there was suggestive evidence of potential human carcinogenicity. (EPA also noted that under its 1986 cancer guidelines, EPA classified naphthalene as a possible human carcinogen.) Subsequently, in 2002, the International Agency for Research on Cancer (IARC), part of the World Health Organization, concluded that naphthalene is possibly carcinogenic to humans; in 2004, the Department of Human Health and Services' National Toxicology Program concluded that naphthalene can reasonably be anticipated to be a human carcinogen. EPA's current assessment will be subject to the agency's 2005 cancer guidelines.

the assessment would have been completed and released. However, in part because of concerns raised by DOD, OMB asked to review the assessment and conducted an interagency review of the draft. In their 2004 reviews of the draft IRIS assessment, both OMB and DOD raised a number of concerns about the assessment and suggested to EPA that it be suspended until additional research could be completed to address what they considered to be significant uncertainties associated with the assessment. Although all of the issues raised by OMB and DOD were not resolved, EPA continued with its assessment by submitting the draft for external peer review, which was completed in September 2004.[10] However, according to EPA, OMB continued to object to the draft IRIS assessment and directed EPA to convene an additional expert review panel on genotoxicity to obtain recommendations about short-term tests that OMB thought could be done quickly.[11] According to EPA, this added 6 months to the process, and the panel, which met in April 2005, concluded that the research that OMB was proposing could not be conducted in the short term. Nonetheless, EPA officials said that the second expert panel review did not eliminate OMB's concerns regarding the assessment, which they described as reaching a stalemate. In September 2006, EPA decided, however, to proceed with developing the assessment. By this time, the naphthalene assessment had been in progress for over 4 years; EPA decided that the IRIS noncancer assessment, issued in 1998, was outdated and needed to be revisited. Thus, EPA expanded the IRIS naphthalene assessment to include both noncancer and cancer assessments. As a result, 6 years after the naphthalene assessment began, it is now back at the drafting stage. The assessment now will need to reflect relevant research completed since the draft underwent initial external peer review in 2004, and it will have to undergo all of the IRIS assessment steps again, including additional internal and external reviews that are now required. This series of delays has limited EPA's ability to conduct its mission. For example, the Office of Air and Radiation has identified the naphthalene assessment as one of its highest-priority needs for its air toxics program. In addition, the Office of Solid Waste and Emergency Response considers the naphthalene assessment a high priority

[10]According to DOD, EPA did not specifically ask the peer reviewers to address some of the technical questions DOD had raised and wanted the peer review to address.

[11]Genotoxic substances are a type of carcinogen, specifically those capable of causing genetic mutation and of contributing to the development of tumors. This includes both certain chemical compounds and certain types of radiation.

for the Superfund program—naphthalene has been found in at least 654 of Superfund's current or former National Priorities List sites.[12] Although EPA currently estimates that it will complete the assessment in 2009, meeting this revised estimate will be challenging, given all of the steps that are yet to be completed and the extensive external scrutiny to which it will continue to be subjected.

Royal Demolition Explosive. This chemical, also called RDX or hexahydro-1,3,5-trinitrotriazine, is a highly powerful explosive used by the U.S. military in thousands of munitions. Currently classified by EPA as a possible human carcinogen, this chemical is known to leach from soil to groundwater. Royal Demolition Explosive can cause seizures in humans and animals when large amounts are inhaled or ingested, but the effects of long-term, low-level exposure on the nervous system are unknown. As is the case with naphthalene, the IRIS assessment could potentially require DOD to undertake a number of actions, including steps to protect its employees from the effects of this chemical and to clean up many contaminated sites. Although EPA started an IRIS assessment of Royal Demolition Explosive in 2000, it has made minimal progress on the assessment because EPA agreed to a request by DOD to wait for the results of DOD-sponsored research on this chemical. In 2007, EPA began to actively work on this assessment, although some of the DOD-sponsored research is still outstanding.

Formaldehyde. EPA began an IRIS assessment of formaldehyde in 1997 because the existing assessment was determined to be outdated.[13] Formaldehyde is a colorless, flammable, strong-smelling gas used to manufacture building materials, such as pressed wood products, and used in many household products, including paper, pharmaceuticals, and leather goods. While EPA currently classifies formaldehyde as a probable human carcinogen, the International Agency for Research on Cancer (IARC), part of the World Health Organization, classifies formaldehyde as a known human carcinogen. Since 1986, studies of industrial of workers have suggested that formaldehyde exposure is associated with nasopharyngeal cancer, and possibly with leukemia. For example, in 2003 and 2004,

[12]The National Priorities List is EPA's list of seriously contaminated sites.
[13]The cancer portion of the formaldehyde assessment was originally issued in 1989 and updated in 1991; the noncancer assessment was added in 1990.

the National Cancer Institute (NCI) and the National Institute of Occupational Safety and Health (NIOSH) released epidemiological studies following up on earlier studies tracking about 26,000 and 11,000 industrial workers, respectively, exposed to formaldehyde; the updates showed exposure to formaldehyde might also cause leukemia in humans, in addition to the cancer types previously identified. According to NCI officials, the key findings in their follow-up study were an increase in leukemia deaths and, more significantly, an exposure/response relationship between formaldehyde and leukemia—as exposure increased, the incidence of leukemia also rose. As with the earlier study, NCI found more cases of a rare form of cancer, nasopharyngeal cancer, than would usually be expected. The studies from NCI and NIOSH were published in 2003 and 2004,[14] around the time that EPA was still drafting its IRIS assessment. In November 2004, the Chairman of the Senate Environment and Public Works Committee requested that EPA delay completion of its IRIS assessment until an update to the just-released NCI study could be conducted, indicating that the effort would take, at most, 18 months. EPA agreed to wait—and more than 3 years later, the NCI update is not yet complete. As of December 2007, NCI estimates that the study will be completed in two stages, one in mid-2008 and the second one later that year. An NCI official said that the additional leukemia deaths identified in the update provide "greater power" to detect associations between exposure to formaldehyde and cancer. EPA's inability to complete the IRIS assessment it started more than 10 years ago in a timely manner has had a significant impact on EPA's air toxics program. Specifically, when EPA promulgated a national emissions standard for hazardous air pollutants covering facilities in the plywood and composite wood industries in 2004, EPA's Office of Air and Radiation took the unusual step of not using the existing IRIS estimate but rather decided to use a cancer risk

[14]NCI published the results of its study in two publications. The first study, published in November 2003, focused on the association between formaldehyde exposure and leukemia. M. Hauptmann, J. H. Lubin, P. A. Stewart, R. B. Hayes, A. Blair, "Mortality from Lymphohematopoietic Malignancies among Workers in Formaldehyde Industries," *Journal of the National Cancer Institute* (2003). The second study, published in June 2004, evaluated the association between formaldehyde exposure and other cancers—including nasopharyngeal cancer. M. Hauptmann, J. H. Lubin, P. A. Stewart, R. B. Hayes, A. Blair, "Mortality from Solid Cancers among Workers in Formaldehyde Industries," *American Journal of Epidemiology* (2004). The results of the NIOSH study were described in one publication, dated March 2004, which assessed mortality from all causes and all cancers. L. E. Pinkerton, M. J. Hein, L. T. Stayner, "Mortality among a Cohort of Garment Workers Exposed to Formaldehyde: an Update," *Occupational and Environmental Medicine* (2004).

estimate developed by an industry-funded organization, the CIIT Centers for Health Research (formerly, the Chemical Industry Institute of Toxicology) that had been used by the Canadian health protection agency. The IRIS cancer risk factor had been subject to criticism because it was last revised in 1991 and was based on data from the 1980s. In its final rule, EPA stated that "the dose-response value in IRIS is based on a 1987 study, and no longer represents the best available science in the peer-reviewed literature." The CIIT quantitative cancer risk estimate that EPA used in its health risk assessment in the plywood and composite wood national emissions standard indicates a potency about 2,400 times lower than the estimate in IRIS that was being re-evaluated and that did not yet consider the 2003 and 2004 NCI and NIOSH epidemiological studies. According to an EPA official, an IRIS cancer risk factor based on the 2003 and 2004 NCI and NIOSH studies would likely be close to the current IRIS assessment, which EPA has been attempting to update since 1997. The decision to use the CIIT assessment in the plywood national emissions standard was controversial, and officials in EPA's National Center for Environmental Assessment said the center identified numerous problems with the CIIT estimate. Nonetheless, the Office of Air and Radiation used the CIIT value, and that decision was a factor in EPA exempting certain facilities with formaldehyde emissions from the national emissions standard. In June 2007, a federal appellate court struck down the rule, holding that EPA's decision to exempt certain facilities that EPA asserted presented a low health risk exceeded the agency's authority under the Clean Air Act.[15] Further, the continued delays of the IRIS assessment of formaldehyde—currently estimated to be completed in 2010 but after almost 11 years still in the draft development stage—will impact the quality of other EPA regulatory actions, including other air toxics rules and requirements.

Trichloroethylene. Also known as TCE, this chemical is a solvent widely used as a degreasing agent in industrial and manufacturing settings; it is a common environmental contaminant in air, soil, surface water, and groundwater. TCE has been linked to cancer, including childhood cancer, and other significant health hazards, such as birth defects.

[15] *Natural Resources Defense Council v. E.P.A.*, 489 F.3d 1364, 1372-73 (D.C. Cir, 2007). The court did not specifically address EPA's reliance on the CIIT study, holding instead that the Clean Air Act prohibited establishment of the exemptions at issue.

TCE is the most frequently reported organic contaminant in groundwater, and contaminated drinking water has been found at Camp Lejeune, a large Marine Corps base in North Carolina. TCE has also been found at Superfund sites and at many industrial and government facilities, including aircraft and spacecraft manufacturing operations. In 1995, the International Agency for Research on Cancer classified TCE as a probable human carcinogen, and in 2000, the Department of Health and Human Services' National Toxicology Program concluded that it is reasonably anticipated to be a human carcinogen. Because of questions raised by peer reviewers about the IRIS cancer assessment for TCE, EPA withdrew it from IRIS in 1989 but did not initiate a new TCE cancer assessment until 1998. In 2001, EPA issued a draft IRIS assessment for TCE that proposed a range of toxicity values indicating a higher potency than in the prior IRIS values and characterizing TCE as "highly likely to produce cancer in humans." The draft assessment, which became controversial, was peer reviewed by EPA's Scientific Advisory Board and released for public comment. A number of scientific issues were raised during the course of these reviews, including how EPA had applied emerging risk assessment methods—such as assessing cumulative effects (of TCE and its metabolites) and using a physiologically based pharmacokinetic model—and the uncertainty associated with the new methods themselves.[16] To help address these issues, EPA, DOD, DOE, and NASA sponsored a National Academies review to provide guidance. The National Academies report, which was issued in 2006, concluded that the weight of evidence of cancer and other health risks from TCE exposure had strengthened since 2001 and recommended that the risk assessment be finalized with currently available data so that risk management decisions could be made expeditiously. The report specifically noted that while some additional information would allow for more precise estimates of risk, this information was not necessary for developing a credible risk assessment. Nonetheless, 10 years after EPA started its IRIS assessment, the TCE assessment is back at the draft development stage. EPA estimates this assessment will be finalized in 2010. More in line with the National Academies' recommendation to act

[16]Physiologically based pharmacokinetic models are a class of dosimetry models that are useful for predicting internal doses to target organs. With the appropriate data, these models can be used to extrapolate across species and exposure scenarios and address various sources of uncertainty in risk assessments.

expeditiously, five senators introduced a bill in August 2007 that, among other things, would require EPA to both establish IRIS values for TCE and issue final drinking water standards for this contaminant within 18 months.

Tetrachloroethylene. EPA started an IRIS assessment of tetrachloroethylene—also called perchloroethylene or "perc"—in 1998. Tetrachloroethylene is a manufactured chemical widely used for dry cleaning of fabrics, metal degreasing, and making some consumer products and other chemicals. Tetrachloroethylene is a widespread groundwater contaminant, and the Department of Health and Human Services' National Toxicology Program has determined that it is reasonably anticipated to be a carcinogen. The IRIS database currently contains a 1988 noncancer assessment based on oral exposure that will be updated in the ongoing assessment. Importantly, the ongoing assessment will also provide a noncancer inhalation risk and a cancer assessment. The IRIS agency review of the draft assessment was completed in February 2005, the draft assessment was sent to OMB for OMB/interagency review in September 2005, and the OMB/interagency review was completed in March 2006. EPA had determined to have the next step, external peer review, conducted by the National Academies—the peer review choice reserved for chemical assessments that are particularly significant or controversial. EPA contracted with the National Academies for a review by an expert panel, and the review was scheduled to start in June 2006 and be completed in 15 months. However, as of December 2007, the draft assessment had not yet been provided to the National Academies. After verbally agreeing with both the noncancer and cancer assessments following briefings on the assessments, the Assistant Administrator, Office of Research and Development, subsequently requested that additional uncertainty analyses—including some quantitative analyses—be conducted and included in the assessment before the draft was released to the National Academies for peer review. As discussed in our March 2008 report on IRIS (GAO-08-440), quantitative uncertainty analysis is a risk assessment tool that is currently being developed, and although the agency is working on developing policies and procedures for uncertainty analysis, such guidance currently does not exist. The draft tetrachloroethylene assessment has been delayed since early 2006 as EPA staff have gone back and forth with the Assistant

Administrator trying to reach agreement on key issues such as whether a linear or nonlinear model is most appropriate for the cancer assessment and how uncertainty should be qualitatively and quantitatively characterized. EPA officials and staff noted that some of the most experienced staff are being used for these efforts, limiting their ability to work on other IRIS assessments. In addition, the significant delay has impacted the planned National Academies peer review because the current contract, which has already been extended once, cannot be extended beyond December 2008. The peer review was initially estimated to take 15 months. As a result, a new contract and the appointment of another panel may be required.

Dioxin. The dioxin assessment is an example of an IRIS assessment that has been, and will likely continue to be, a political as well as a scientific issue. Often the byproducts of combustion and other industrial processes, complex mixtures of dioxins enter the food chain and human diet through emissions into the air that settle on soil, plants, and water. EPA's initial dioxin assessment, published in 1985, focused on the dioxin TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) because animal studies in the 1970s showed it to be the most potent cancer-causing chemical studied to date. Several years later, EPA decided to conduct a reassessment of dioxin because of major advances that had occurred in the scientific understanding of dioxin toxicity and significant new studies on dioxins' potential adverse health effects. Initially started in 1991, this assessment has involved repeated literature searches and peer reviews. For example, a draft of the updated assessment was reviewed by a scientific peer review panel in 1995, and three panels reviewed key segments of later versions of the draft in 1997 and 2000. In 2002, EPA officials said that the assessment would conclude that dioxin may adversely affect human health at lower exposure levels than had previously been thought and that most exposure to dioxins occurs from eating such American dietary staples as meats, fish, and dairy products, which contain minute traces of dioxins. These foods contain dioxins because animals eat plants and commercial feed and drink water contaminated with dioxins, which then accumulate in animals' fatty tissue. It is clear that EPA's dioxin risk assessment could have a potentially significant impact on consumers and on the food and agriculture industries. As EPA moved closer to finalizing the assessment, in 2003 the

agency was directed in a congressional appropriations conference committee report to not issue the assessment until it had been reviewed by the National Academies. The National Academies provided EPA with a report in July 2006. In developing a response to the report, which the agency is currently doing, EPA must include new studies and risk assessment approaches that did not exist when the assessment was drafted. EPA officials said the assessment will be subject to the IRIS review process once its response to the National Academies' report is drafted. As of 2008, EPA has been developing the dioxin assessment, which has potentially significant health implications for all Americans, for 17 years.

Appendix II: Summary of Two GAO Reports on EPA's Toxic Substances Control Act and Chemical Control Regulations in the European Union

This appendix summarizes information presented in two prior GAO reports and related work on EPA's regulation of toxic chemicals. In 1976, Congress passed the Toxic Substances Control Act (TSCA) to authorize the Environmental Protection Agency (EPA) to obtain information on chemicals and regulate chemicals that pose an unreasonable risk to human health or the environment. In 2005, we reviewed EPA's efforts to assess the risks of new chemicals—those not yet in commerce—and the risks of existing chemicals—those already being used in commerce.[17] In summary, EPA faces challenges in obtaining the information necessary to assess the human health and environmental risks of chemicals.

Like the United States, the European Union has laws governing the production and use of chemicals. The European Union has recently revised its chemical control policy through legislation known as Registration, Evaluation and Authorization of Chemicals (REACH). In another report, we provided comparative information on TSCA and REACH.[18] In summary, REACH generally requires that chemical companies develop and provide government regulators with information on chemicals' effects on human health and the environment, while TSCA generally does not. REACH is based on the principle that chemical companies have the responsibility to demonstrate that the chemicals they place in the market, distribute, or use do not adversely affect human health or the environment, while TSCA generally requires EPA to demonstrate that chemicals pose risks to human health or the environment prior to controlling risks related to their production, distribution, or use. The findings of these reports are summarized below.

[17]GAO, *Chemical Regulation: Actions Are Needed to Improve the Effectiveness of EPA's Chemical Review Program*, GAO-06-1032T (Washington, D.C.: Aug. 2, 2006); and GAO, *Chemical Regulation: Options Exist to Improve EPA's Ability to Assess Health Risks and Manage Its Chemical Review Program*, GAO-05-458 (Washington, D.C.: June 13, 2005).

[18]GAO, *Chemical Regulation: Comparison of U.S. and Recently Enacted European Union Approaches to Protect against the Risks of Toxic Chemicals*, GAO-07-825 (Washington, D.C.: Aug. 17, 2007); and GAO, *Chemical Regulation: Approaches in the United States, Canada, and the European Union*, GAO-06-217R (Washington, D.C.: Nov. 4, 2005).

Key Findings in GAO's 2005 Report and Related Testimony

Overall, we found that EPA has limited information on the health and environmental risks of chemicals. EPA does not routinely assess the human health and environmental risks of existing chemicals and faces challenges in obtaining the information to do so. TSCA's authorities for collecting data on existing chemicals do not facilitate EPA's review process because they generally place the costly and time-consuming burden of obtaining data on EPA, rather than requiring chemical companies to develop and submit such data to EPA. Consequently, EPA has used its authorities to require testing for few of the over 60,000 chemicals already in commerce when EPA began reviewing chemicals under TSCA in 1979. Recognizing the need for additional information on existing chemicals, EPA has initiated voluntary programs. While these programs are a laudable effort to develop data on these chemicals, several problems remain, including that the chemical industry may not provide testing results in a timely manner for all chemicals in these programs and that even with additional test data, EPA would need to demonstrate that the chemicals pose unreasonable risks in order to control their production or use under TSCA. While TSCA does not define what risk is unreasonable, EPA has found it difficult to meet this standard. In order to withstand judicial scrutiny, a TSCA rule must be supported by substantial evidence in the rule-making record. In this regard, EPA officials say the act's legal standards are so high that they have generally discouraged EPA from using its authorities to ban or restrict the manufacture or use of chemicals.

Further, EPA's reviews of new chemicals can provide only limited assurance that health and environmental risks are identified before the chemicals enter commerce because TSCA does not require chemical companies to test new chemicals before notifying EPA of their intent to manufacture a chemical. Furthermore, chemical companies generally do not voluntarily perform such testing. Because of a general lack of data, EPA has developed scientific models to predict the potential exposure and toxicity levels of new chemicals. However, the use of these models can present weaknesses in the assessment because the models are not always accurate in predicting physical chemical properties and the evaluation of general health effects is contingent on the availability of information on chemicals with similar molecular structures. Additionally, chemical

company estimates of a chemical's production volume and anticipated uses provided in the premanufacture notices that EPA uses to assess exposure can change substantially after EPA completes its review and manufacturing begins. However, these estimates do not have to be amended by companies unless EPA promulgates a rule determining that a use of a chemical constitutes a significant new use, which EPA has done for only a small percentage of new chemicals. Despite limitations in the information available on new chemicals, EPA's reviews have resulted in some action being taken to reduce the risks of over 3,600 new chemicals submitted for review.

EPA's ability to provide the public with information on chemical production and risk has also been hindered by strict confidential business information provisions of TSCA, which generally prohibits the disclosure of confidential business information. According to EPA officials, about 95 percent of the premanufacture notices for new chemicals contain some information that is claimed as confidential. While EPA has the authority to evaluate the appropriateness of confidentiality claims, these efforts are time and resource-intensive, and the agency does not have the resources to challenge a significant number of claims. State environmental agencies and others have expressed interest in obtaining information claimed as confidential business information for use in various activities, such as developing contingency plans to alert emergency response personnel to the presence of highly toxic substances at manufacturing facilities. Chemical companies recently have expressed interest in working with EPA to identify ways to enable other organizations to use the information given the adoption of appropriate safeguards.

In our June 2005 report, we recommended that Congress consider providing EPA with additional authorities under TSCA to improve its ability to assess chemical risks, such as providing the EPA Administrator with the authority to require that chemical companies develop test data when production volumes reach certain levels. We also recommended that the EPA Administrator take several actions to improve EPA's management of its chemical program, including revising its regulations to require that companies reassert confidentiality claims under TSCA within a certain time period after the information is

initially claimed as confidential. EPA did not disagree with the report's findings and is in the process of implementing several of our recommendations.

Key Findings in GAO's 2007 Report and Related Correspondence

Overall, we found that REACH, the legislation through which the European Union has recently revised its chemical control policy, requires chemical companies to develop more information than TSCA on the effects of chemicals on human health and the environment. REACH generally requires that chemical companies develop and provide government regulators information on chemicals' effects on human health and the environment, while TSCA generally does not. For example, under REACH, chemical companies provide, and in some cases develop, information on chemicals' physical/chemical properties and health and environmental effects for both new and existing chemicals produced over specified volumes. REACH also provides regulators the general authority to require chemical companies to provide additional test data and other information when necessary to evaluate a chemical's risk to human health and the environment. In contrast, TSCA places the burden on EPA to demonstrate that data on health and environmental effects are needed before requiring chemical companies to develop the data. In this regard, while TSCA requires chemical companies to notify EPA before producing or importing a new chemical, it does not require chemical companies to develop and provide data on health and environmental effects unless EPA promulgates a rule requiring them to do so. In promulgating such a rule, EPA must demonstrate that data already available are insufficient and that either (1) the chemical may present an unreasonable risk or (2) the chemical is or will be produced in substantial quantities and that there is or may be substantial human or environmental exposure to the chemical.

REACH is based on the principle that chemical companies have the responsibility to demonstrate that the chemicals they place in the market, distribute, or use do not adversely affect human health or the environment, while TSCA generally requires EPA to demonstrate that chemicals pose risks to human health or the environment prior to

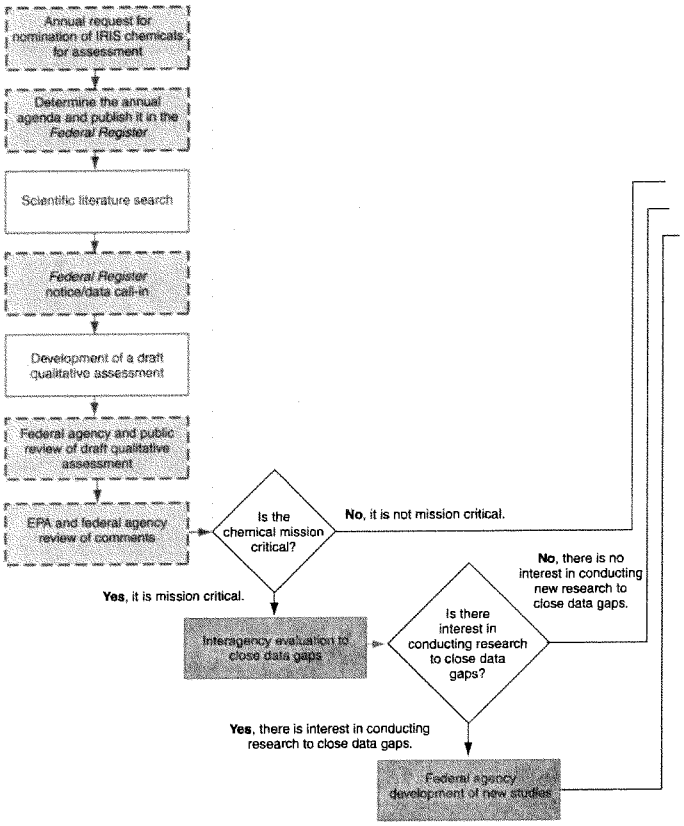
controlling risks related to their production, distribution, or use. Under REACH, chemical companies must obtain authorization to continue to use a chemical of very high concern, such as a chemical for which there is scientific evidence of probable serious health or environmental effects. Generally, to obtain such authorization, each chemical company needs to demonstrate that it can adequately control risks posed by the chemical, such as by requiring that workers wear safety equipment when working with the chemical or otherwise ensuring that the chemical is produced under safe conditions. If the chemical company cannot provide evidence of adequate control, authorization would be granted only if the socioeconomic advantages of a specific use of the chemical are greater than its potential risks, and if there are no suitable alternatives or technologies.

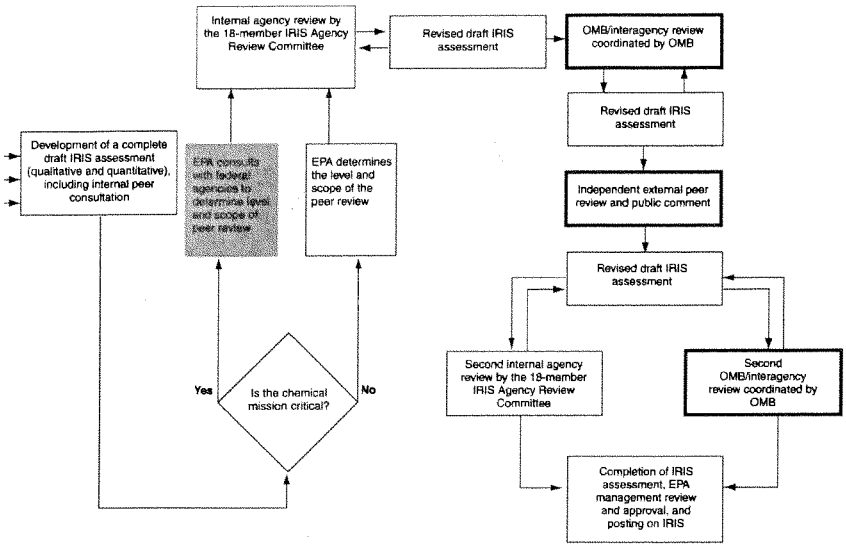
Under TSCA, EPA has differing authorities to control the risks posed by new and existing chemicals. For new chemicals, EPA can restrict a chemical's production or use if the agency determines that insufficient information exists to permit a reasoned evaluation of the health and environmental effects of the chemical and that, in the absence of such information, the chemical may present an unreasonable risk to human health or the environment; the chemical is or will be produced in substantial quantities and either enters or may reasonably be anticipated to enter the environment in substantial quantities; or there is or may be significant or substantial human exposure to the substance. For existing chemicals, EPA may regulate those chemicals for which it finds a reasonable basis exists to conclude that they present or will present an unreasonable risk to human health or the environment. In this regard, EPA can promulgate a rule that bans or restricts the chemical's production, processing, distribution in commerce, use, or disposal, or that requires warning labels be placed on the chemical. However, TSCA requires EPA to choose the least burdensome requirement on the chemical industry that will adequately protect against the risk.

TSCA and REACH both have provisions to protect information claimed by chemical companies as confidential or sensitive business information; however, REACH requires greater public disclosure of certain information, including information about (1) basic

chemical properties such as melting and boiling points and (2) analytical methods that make it possible to detect a dangerous substance when discharged into the environment and to determine the effects of direct exposure to humans. In addition, REACH places greater restrictions on the kinds of information companies may claim as confidential or sensitive. For example, REACH generally does not allow confidentiality claims to apply to the chemical's trade name, and it does not allow such claims to apply to guidance on the chemical's safe use.

Appendix III: EPA's IRIS Assessment Process as of April 10, 2008





Darker shaded boxes are additional steps under EPA's changes to its assessment process and indicate where EPA has provided additional opportunity for input from potentially affected federal agencies for mission-critical chemicals.

Lighter shaded boxes with dotted lines indicate steps where EPA has provided additional opportunity for input from potentially affected federal agencies for all chemicals.

White boxes with heavy lines indicate steps where potentially affected federal agencies already had an opportunity for input.

Source: GAO analysis of EPA information.

(360955)

Senator BOXER. Thank you very much.

We will do 5-minute rounds and probably have two rounds.

Mr. Gulliford, what chemicals have you banned or regulated under TSCA that were not voluntary withdrawn or regulated by the industry or by Congress since you took over?

Mr. GULLIFORD. Thank you, Madam Chair.

We regulate and take regulatory actions related to chemicals almost daily. Every year, we receive about 1,200——

Senator BOXER. No, no, no, I——

Mr. GULLIFORD [continuing].—for new chemicals——

Senator BOXER. I am not asking you that. How many have you, in your position, chemicals have you either regulated or banned without them being withdrawn or regulated by the industry itself or banned or regulated by Congress? Do you have that number off the top of your head?

Mr. GULLIFORD. The actions that we take, our actions at EPA, do reflect our work, which in effect has the impact of determining whether chemicals are brought into production or not.

Senator BOXER. I know, but I'm asking you——

Mr. GULLIFORD. Those are regulatory actions.

Senator BOXER [continuing].—for a specific answer. And so you don't have it. So will you please send to me in writing the lists and names of chemicals that under TSCA, since you took over, have been either banned or been regulated other than those that the industry itself decided to do or Congress took into its own hands, which we have done. So if you could do that, I would be really appreciative. I understand the process. I am trying to get to what have you done in your position.

[The referenced material follows:]

Senator BOXER. Now, Mr. Stephenson, the GAO report states "The farther removed the scientists and experts who have prepared or peer-reviewed the assessments are from the negotiations and decisions over assessment changes requested by OMB and other Federal agencies, the decisions are based more on political rather than scientific considerations." I think that is important, because Senator Craig kind of accused this Committee of playing politics. The whole point is, the GAO report says that there is political considerations.

So how important is it to ensure that IRIS assessments are based on solid science rather than political considerations?

Mr. STEPHENSON. According to the National Academies, there are two components there is a risk assessment part and there is the risk management part. The management part is where you consider political input or other circumstances, you do cost benefit analysis and decide regulatory approaches.

However, in the risk assessment process, you don't want——

Senator BOXER. That is what I am talking about.

Mr. STEPHENSON [continuing].—anybody but scientists involved.

Senator BOXER. Right. That is the point.

Mr. STEPHENSON. That is our major problem with the lack of transparency and the new process is that any comments that EPA receives from either the Department of Defense, NASA or OMB itself are withheld from the public.

Senator BOXER. That is the second question. But the first point I want to reiterate that you made, I think it is critical here, is that in the risk assessment part of this, it should be pure. It should be about the health of people, is that right?

Mr. STEPHENSON. Absolutely.

Senator BOXER. Absolutely. OK, that is No. 1.

Now, second, the secrecy which you raised. My understanding is, in your report you say that the comments made by these other entities are kept secret by the White House. You find a problem with that, I certainly find a problem with that. Why do you think this is the case? Do you have any thoughts?

Mr. STEPHENSON. I think that the OMB is muddling the two parts of the process. They are getting involved in the science portion, the early assessment of chemicals, when they should be getting involved in the later, what should the regulatory approach be, what is the least burdensome approach we can do to regulate this chemical. They should not be muddling in the front part, in the science.

Senator BOXER. OK. Mr. Gulliford, doesn't EPA's Office of Prevention, Pesticides and Toxic Substances rely on information from IRIS in their work to help prevent, to help protect public health?

Mr. GULLIFORD. With respect to our chemicals program, yes. There are a number of the IRIS characterizations that are important to us. Through our ChAMP work, we are looking at doing well over 7,000 chemical assessments.

Senator BOXER. But I am just trying to get at the point about IRIS here. So you do, in some cases rely on IRIS?

Mr. GULLIFORD. We have asked that certain chemicals be studied under IRIS and taken through the IRIS process.

Senator BOXER. Good. That is an important point. So don't you want to ensure that your office uses the best available science to protect public health and not secret information that is tainted by outside interests?

Mr. GULLIFORD. We do that every day. We utilize the best science that is available——

Senator BOXER. Well, you count on IRIS, you count on the IRIS program for certain of these, and we have been told by the GAO, not by me or anybody else, that politics is in the process. So when you now hear, you get your information ipso facto, if GAO is right, and I tend to believe them, they have a reputation for integrity and they have no axe to grind here, you are getting tainted information. And that is a problem.

Senator BARRASSO.

Senator BARRASSO. Thank you very much, Madam Chairman.

Early you mentioned about my background and training as an orthopedic surgeon. The derivative of orthopedics comes from the Greek, and it is the word ortho, meaning straight, and paedos, meaning child. So lots of the training I do is with children and I have very significant concerns in those areas.

Mr. Gulliford, if I could, I mentioned earlier this Washington Post story about all the advances in children and kind of getting the lead out of the system. Isn't that something EPA should take credit for?

Mr. GULLIFORD. EPA has worked with HUD and with other agencies for many years on issues of lead. We are very pleased that, for example, or the last 20 or so years ago, we have gone from as many as 3 million children affected by elevated blood levels to now where CDC estimates roughly 300,000. We are also very pleased with our new lead rule, which we believe will actively help again to prevent exposures to lead.

Senator BARRASSO. When you look at exposures in terms of assessing risk to humans, don't you really assume the worst case scenarios in terms of an exposure and try to stay below those numbers?

Mr. GULLIFORD. We look for realistic exposure estimates. We build in safeguards to assure that we don't approach those exposure thresholds that we believe are dangerous or threatening.

Senator BARRASSO. If we take a look at this one size fits all approach to so many things I see happening in Washington here, if you used that approach to every chemical under TSCA, wouldn't you end up wasting a lot of your time on some low priority chemicals and really deflecting from the real issues affecting our children?

Mr. GULLIFORD. We absolutely would be. One of the things that I believe is most important is that we find a way to prioritize our work, to identify those chemicals of concern with respect to health of children, adults, all our people and the environment. That is why in our ChAMP program, we have developed a prioritization process to identify those chemicals and then follow up with industry to assure that exposure of those chemicals does not occur either to workers or the environment or to people that use products that are produced from the use of those chemicals.

Senator BARRASSO. So I take it then that you don't always agree with the chemical industry, or shall I say the chemical industry doesn't always agree with you?

Mr. GULLIFORD. No, absolutely not. Our work is to evaluate the data that they give us and make independent decisions by the agency, rather than to allow industry alone to make decisions.

Senator BARRASSO. Thank you, Madam Chairman.

Senator BOXER. Thanks. I just want to let the record show that the lead, the progress on lead was made under the old rules, which is what we are trying to defend here today. And that will show, because that is one of the good things that happened under the old way.

Senator Whitehouse.

Senator WHITEHOUSE. Thank you, Madam Chair. I am not sure it is part of the record, so I would just like to start by showing Mr. Gulliford the picture of the IRIS process. I believe we got this from EPA staff. And I just want to make sure that this is correct.

It shows, before 2004, an IRIS process that was already pretty——

Senator BOXER. Would you bring that over to Senator Whitehouse and show it——

Senator WHITEHOUSE. And then, well, hold on a second.

Senator BOXER. That is the new one. Where is the old one?

We don't have it. So show that old one, and then we will show the new one.

Senator WHITEHOUSE. It starts already looking pretty complicated with 11 steps here. Then from 2004 to 2008, it started to look more like this, it went from 11 to 15 steps——

Senator BOXER. That is the one.

Senator WHITEHOUSE [continuing].—and became every more complicated. And now the draft process looks like this and has all sorts of, I can't count the number of steps and sub-steps that it has. It just looks to the lay viewer as if this process is getting more complicated and cumbersome.

In addition, I am concerned about the role that OMB plays being injected into the process relatively early on. What scientific expertise does the Office of Management and Budget bring to the table in these discussions about risks of chemicals?

Mr. GULLIFORD. Let me start with your first question and your comment on the complexity. That board also can demonstrate the fact that an effort is being made to be more explicit about all of the steps and to further or better define them, as well as perhaps adding steps. So there are a couple of things in effect there.

OMB has scientists and economists and professionals that work for them as well. Their role principally, though, is to assure effective interagency review. It happens with rules, it happens with other programs. And the agency does believe that in the IRIS process, interagency review, opportunity for interagency input into the process, as well as public input, public review and finally science review as well by third party outside scientists, all of those are important parts of the IRIS process.

Senator WHITEHOUSE. Should we have concern about the private nature, the non-public nature of OMB's review? As I understand if, it you are an American company who wants to comment on this, on a piece, on an administrative process, a chemical that is being put through the IRIS process, your comments have to be public. And if you are an American advocacy group, if you are the Heart Association or the Cancer Society and you want to comment on it, your comments have to be public. And if you are an American mom or citizen who wants to comment on it, your comments have to be public.

The carve-out is for other Federal agencies. And what it seems to create is a loophole where, if you want to influence this process and you don't want to say it publicly, you go to a White House, you get them to tell OMB what to do, because it is part of the White House, and you can stick whatever comments you want in, and it is a way to launder comments you wouldn't make publicly through politics and into this. Isn't that a legitimate concern?

Mr. GULLIFORD. That is an assumption that you are making. I am not certain that would or wouldn't happen. I don't believe that it would.

Senator WHITEHOUSE. Is there anything in the process that would prevent that from happening?

Mr. GULLIFORD. There is the allowance for the agency to review mission-critical chemicals and that be a protected process.

Senator WHITEHOUSE. How does that keep OMB out, if OMB has been made amenable to political——

Mr. GULLIFORD. You are making the assumption that OMB is made amenable to that political process, in the Office of Management and Budget for interagency review, as I had stated earlier.

Senator WHITEHOUSE. You know, one of the things we do in American Government is we have things be transparent and aboveboard so we can prevent things from happening. So it is usually wise, when you see a system that create an avenue for that kind of politics to happen, to press on it and try to figure out why the system wouldn't protect itself against that. If you leave a door open to that, I don't think it is an adequate public protection to say, well, we can't prove that it is being used for that purpose is because the very process keeps it private and confidential and out of the public view, allows it to be done behind closed doors. That doesn't seem right, does it?

Mr. GULLIFORD. The final products of the IRIS process are reviewed by third party science organizations. That is the purpose, that ultimately, when EPA has gone through the process, EPA has heard input from the public, EPA has heard input from agencies, EPA has heard, people have been given the opportunity under this process to bring data, bring information, to bring opinion to the process, ultimately it is still, at the end of the day, it is EPA's decision. EPA makes the determinations on those final IRIS characterizations. And then they are split out for third party review.

So I believe it is a transparent process. It is a process that ultimately results in a science-based result.

Senator WHITEHOUSE. Madam Chair, my time has expired.

Senator BOXER. Yes. I thank you, Senator. I just want to say, Mr. Gulliford, and you are a very good witness, but Senator Whitehouse is not the one making these charges. GAO said this thing is so secret they talked about a black box, that this information that you say is public is never public. It is actually in a black box, it is secret.

So when you say to Senator Whitehouse that he is not correct, he is relying on the investigation of this process.

Mr. GULLIFORD. I apologize. Senator Whitehouse asked the question, that is why——

Senator BOXER. I understand, but I just want to make sure that we understand the GAO makes this point. It is not an individual Senator. He is just reiterating what we now know is the truth about the process.

Senator CRAIG.

Senator CRAIG. Thank you, Madam Chair.

Gentlemen, thank you very much for your testimony. I am trying to understand the process, because it appears that it is the process that is under attack today and not the outcome. I think we are obviously concerned about transparency. We are also very concerned about outcome.

Something that has not been mentioned, and I ask you, Mr. Gulliford, does it fit into the process, and that is, how many premanufacturing notices has the EPA received versus notices to commence? Now, the reason this is important, when we are talking about propriety and ownership of product and development of product, part of the value of the ownership is the chemistry and the formula.

But it is important to understand that as it relates to human health and understanding. So the question then is, because it appears that in pure transparency you get nothing done, because someone else can steal your work product. At the same time, you want to make sure your work product, the end process, is safe for human consumption and association.

So the question again is, how many pre-manufacturing notices has EPA received versus notices to commence, meaning to commence production once the process is completed? Could you respond to that?

Mr. GULLIFORD. We get about 1,200 PMNs each year.

Senator CRAIG. And a PMN is?

Mr. GULLIFORD. Pre-manufacturing notice. I am sorry.

Senator CRAIG. Thank you. Use common language for us, would you please.

Mr. GULLIFORD. I appreciate that. Since TSCA, roughly 47,000 of those PMNs. We have added 21,000 new chemicals to the chemical inventory, which means that during that process, during our regulation of those notices, our evaluation of those chemicals, our concerns for those chemistries, our interaction with those companies, because as you say, much of that is confidential business information. Those chemicals are either withdrawn because, by our work with them, they have come to the conclusion that they are not an appropriate chemical for us, or ultimately some of them do make it through the process, roughly, I think 21,000 since TSCA.

Senator CRAIG. But percentage-wise, I understand it is around the 50 percent mark.

Mr. GULLIFORD. Or less.

Senator CRAIG. Or less. Those who are, that which is submitted for testing and oversight, or review, through the process, versus that which actually makes it to the market. And often they are withdrawn, are they not?

Mr. GULLIFORD. That is correct.

Senator CRAIG. For future research to meet the compliance standards that you say they must meet.

Mr. GULLIFORD. That is correct.

Senator CRAIG. I see. I guess my next question, because Mr. Stephenson says we ought to stand down and review, I think I understand you right, and reapproach IRIS differently, and in that, you have referenced REACH. REACH, of course, is what the European Union uses. So that is your observation.

So let me ask a question, Mr. Gulliford, has EPA examined REACH and its thoroughness or its responsiveness? Because it is being touted here today as something that is working or is more transparent or is more inclusive, versus what you are doing. And first of all, let me ask you that. I understand there are about 30,000 chemicals that the EU will need to register. How do you think it compares? We have already heard from Mr. Stephenson about he thinks it compares.

Mr. GULLIFORD. REACH is a regulatory chemical management scheme that is now in place in the EU. It is just now beginning to collect the information that is required, the testing, the data that will be developed by industry for their estimate again is

roughly 30,000 chemicals. We will see how many are actually produced by them and submitted.

So at this point in time, they are still in the data development and information development testing mode, and as of yet, decisions under REACH with respect to chemicals have not been made.

Senator CRAIG. So from your point of view, you don't know that a conclusion can be drawn as to its effectiveness?

Mr. GULLIFORD. I think it will be. The effectiveness of REACH will at some point in time be known and evaluated and we will see the benefits of it.

Senator CRAIG. Now, I have portrayed what I think you said, Mr. Stephenson, to be fair. Your reaction to the comment of Mr. Gulliford.

Mr. STEPHENSON. If I could clarify.

Senator CRAIG. Please do.

Mr. STEPHENSON. TSCA is the regulatory approach.

Senator CRAIG. I understand.

Mr. STEPHENSON. We are talking about——

Senator CRAIG. Well, we are not sure what we are talking about.

Mr. STEPHENSON. We are talking about standing down the toxicity assessments under the IRIS program, which is a forerunner of regulation. You have to determine how toxic a chemical is, first.

Senator CRAIG. I understand.

Mr. STEPHENSON. We have other problems with TSCA in that it is cumbersome, it requires a two to 10 year test rule in order to get information from the chemical industry, information that is already provided up front under REACH from the chemical industry. So we are kind of mixing apples and oranges here.

Senator CRAIG. But in our observation, or excuse me, in your observation of REACH, which is a new program in the EU to attempt to register and to clarify the value of or the problems with 30,000 chemicals, can you at this time assess its quality of work and production and its time lines?

Mr. STEPHENSON. It is probably too soon to tell, except that we get much more information, the Government gets much more information from the industry with REACH than it currently does under TSCA without heroic efforts. And it is more of a partnership with the industry, because the industry understands what information it must provide to the regulatory agency. The chemical companies here that do business in Europe must subscribe to REACH. So it is not foreign for them to handle that regulatory framework.

Senator CRAIG. So in other words, is it reasonable to assume then, in REACH, I can't condemn it yet because I don't know about it, or we don't have a track record of its effectiveness, where we have chemical companies——

Senator BOXER. Senator Craig, I just—I am not going to stop you——

Senator CRAIG. This is the last question.

Senator BOXER. No, no, no, let me finish. I will give you an extra 2 minutes, because I think we will have a second round in a few minutes, so you can use your second round now.

Senator CRAIG. Then wouldn't it be responsible for us, instead of throwing the baby out with the bath water, to look at our process and REACH, once it is implemented, through the eyes of, in part,

of the chemical companies that have to deal with both and see which one is the most effective, the most transparent, assures proprietaries needs necessary for a chemical industry to exist and assures human safety.

Mr. STEPHENSON. We are not subscribing the REACH approach. What we have done over the last few years is look at TSCA and talk about how it is cumbersome to use and how it needs overhauling. We have made specific recommendations on our legislation, our regulatory approach, on things that need to be improved. All we are suggesting is that REACH offers a model for front-end information from the chemical industry that we might consider as we overhaul TSCA.

Senator CRAIG. Thank you. Gentlemen, thank you much.

Senator Klobuchar, if you want, I will give you 7 minutes, that would cover your next round.

Senator KLOBUCHAR. No, I am just fine.

Thank you to both of you. I want to follow up on some of Senator Craig's questions with you, Administrator Gulliford, about the European Union. What I understand, regardless of the effectiveness in the long term, is that they are going to be receiving a tremendous amount of information on the safety of chemicals in the coming years under this new law, which is REACH, which standards for Registration, Evaluation, Authorization and Restriction of Chemical Substances. So is the EPA going to request this information on chemical risks from the European program to make sure that our Country has this same up to date and current information that they are going to have in Europe?

Mr. GULLIFORD. Thank you, Senator, that is a very good question. In fact, we are working now with the EU members, with the EU Commission to make sure that there is a portal that allows for access of that information.

Now, having said that, we believe that it is appropriate for us to determine through our process which chemicals we believe are most appropriate for our work, for our follow up actions with respect to those chemistries. We do believe that if the REACH process follows through and generates the data that we expect that it will, at a certain point in time, because I said to you, we would be committing to completing our prioritization work by the year 2012, that we will have at that time an opportunity to select from that data that is available through REACH. So it is possible that we will use that data. But it is also very probable, there are those 30,000 chemicals, there will be a lot of those that we won't find a need for that data as well.

Senator KLOBUCHAR. So are you going to get that data in the next month, or when are we going to get it? We have a panel coming up that is concerned about the health risks here. I know we are working through with the EU, but I would think we would want that immediately. We have good relations with them.

Mr. GULLIFORD. It is industry's obligation to transmit that data to the EU between the timeframe of, I believe 2010 and 2018. So as that data is transmitted, we will know its availability. We will also be able to again, by looking at the work that we propose to do, not on 30,000 chemicals by on our high production or moderate production volume chemicals, roughly 7,000, we will have identified

the chemicals that we believe are most appropriate for action. We will be able to go after that data if we do believe that it will be helpful to us.

Senator KLOBUCHAR. But wouldn't you just rather get the data ourselves than have to go through the EU? It seems to me, just getting to Mr. Stephenson's point, that we should be, the agency itself, which knows the most about this law, should be pushing to update our laws so we get that information.

Mr. GULLIFORD. We will have access to the data when we need it. I think it is more appropriate—it is not our interest to be a data manager, it is to be a data user. I think the most important thing that we can do at EPA is utilize valuable data when we need it in a way that allows us to make effective decisions.

Senator KLOBUCHAR. OK. Mr. Stephenson, do you feel it is fair to say that agency officials in Europe are going to have access to more information on potential threats from chemicals when their new law kicks into gear than we will have in the United States?

Mr. STEPHENSON. It does under the old law, and they will get more under the new law. There is a table in the back of one of our TSCA reports that does a side by side comparison of what we get under TSCA versus what we get under REACH and the Canadian approach, for that matter.

Senator KLOBUCHAR. And what types of information, I will go back and look at that table, but could you give me the greatest hits of information they are going to have?

Mr. STEPHENSON. It is characteristics of the chemicals, but it is also any risk assessment data they have done, any tests they have undertaken. They certify to all that data before it is provided, before a chemical is approved for production.

Senator KLOBUCHAR. Could you talk a little bit about the, earlier you mentioned the need to update these laws, including adequate testing of chemicals, how can we expand that authority under TSCA, if we were to look at revamping this law?

Mr. STEPHENSON. Are you talking about TSCA or the risk assessment process?

Senator KLOBUCHAR. The risk assessment process.

Mr. STEPHENSON. The risk assessment process, again, TSCA is a regulatory approach. We are concerned with the scientific basis for the regulations that is the IRIS program. We are so concerned about OMB involvement here that not only are the comments from the interagency review process not given to the public like every other piece of science input is given, but they are actually dictating which assessments EPA can undertake. They had them withdraw five that the Clean Air Office wanted.

Senator KLOBUCHAR. They had them withdraw, what was that?

Mr. STEPHENSON. Withdraw assessments on five chemicals that were needed by the Office of Clean Air, because they were acute assessments, which means short-term assessments that the Clean Air Office needed for its Air Toxics program, for example. Mr. Gulliford said he uses the data in IRIS and suggests studies that were being done. Well, that is exactly what happened, the Clean Air Office asked for these, OMB said no, they are not important, we are not going to do those.

So it's not only the transparency in the commenting process that is important, it is EPA's independence in controlling which assessments they do. The scientists at EPA must have independence.

Senator KLOBUCHAR. And you believe that the transparency, I believe as a child of a journalist that transparency is very important if you want to get to the truth.

Mr. STEPHENSON. It is a principle of sound science.

Senator KLOBUCHAR. Right, that kind of transparency. It is also going to get at decisions that they make, because you think that we want to, and Mr. Gulliford claims they are not biased in any direction, but that if we want to get all that information out there we have to basically open it up.

Mr. STEPHENSON. Right.

Senator KLOBUCHAR. Do you have other examples of other agencies from a GAO perspective where they are allowing for these comments to be seen?

Mr. STEPHENSON. Well, in any scientific risk assessment, ask the National Academy, ask the National Science Foundation, any scientific body understands the importance of any research that is offered, any comments that are made on the risk assessment to be available to the public, so the scientific community can look at those and decide their worth.

The fact that after that process is done, it is offered to peer review and the public, doesn't forgive that transparency in the earlier part of the process. So it is just a cornerstone of sound science, and that is why we are so passionate about this intervention in the process.

Senator KLOBUCHAR. I appreciate it, and I also appreciate your bringing this out to us in your own manner. I just, when I look at the history that we have seen in this Committee with the involvement in some of the politics in this science, I have always appreciated how people have been willing to come forward and tell us we could do a better job if we just had all the information out there. I am very hopeful that will change within the next year. Thank you.

Senator BOXER. Thank you.

Here is what we are going to do. We are going to have a second round, and we will start with Senator Barrasso, go to Senate Whitehouse, 2 minutes each. And I don't have any further questions, so I will just make closing remarks.

But before Senator Klobuchar leaves, we just got word that a Federal judge has found the Bush administration guilty of violating the Endangered Species Act and ordered the Administration to issue a final listing decision for the polar bear by May 15th. The reason I bring it up is that this Committee has been on this case for quite a while. I wanted everyone to know that. I am pleased about that.

Senator Barrasso.

Senator BARRASSO. Thank you, Madam Chair.

Mr. Gulliford, just one last question. On products that are already on the market, when it comes to issues of safety risks for our children, does the EPA have the appropriate authority under TSCA to go back and require new information, promote research, require

testing on products already on the market? Do you feel you have the authority to go do what needs to be done?

Mr. GULLIFORD. Yes, we do have the authority to issue test rules, yes.

Senator BARRASSO. Thank you, Madam Chairman.

Senator BOXER. Senate Whitehouse. Senator Whitehouse, I will give you a minute of my 2 minutes, so you have three.

Senator WHITEHOUSE. As I understand it, OMB gets involved at the very get-go when nominations as to what drug will be considered are first brought forward. Is that what you were referring to, Mr. Stephenson, the early decision?

Mr. STEPHENSON. I don't know whether that happens routinely, but it has happened.

Senator WHITEHOUSE. Yes. It looks like there is room for it right in the process to happen routinely. Then there is an OMB interagency review which I think is what we were referring to, Mr. Gulliford was referring to a minute ago when he said that it was then followed by other public comments on review and that provided for some transparency, because you couldn't see what they said, you could at least see what change resulted.

But it looks to me like when you get down here to the bitter end, here is OMB again with a second bite at the apple, and from there it goes to a reviewed internal assessment that address the OMB interagency comment to the EPA for clearance and out without any further comment. So I don't see how it is true, what you told me, that after the secret OMB input is received, there is further opportunity for transparency. It looks like that they get the last bite at the apple, don't they?

Mr. STEPHENSON. Are you asking me?

Senator WHITEHOUSE. I am asking Mr. Gulliford.

Mr. GULLIFORD. I am not familiar with that chart, as I indicated, and I would have to examine it to answer that question. I will be happy to take that question back and provide the Committee with an answer to that.

Senator WHITEHOUSE. OK. I would appreciate it. Mr. Stephenson?

Mr. STEPHENSON. The final assessment is shared with the public who can then look at the research, but you can't see what happened in the steps prior to that. You can't say, the DOD offered a new piece of research or something, you can't see what that was. If they had a concern, you don't know what it was. This is the scientific process.

The policymaking process is the risk management, when you are assigning regulatory approaches. It has no business in this part of the process. Now, OMB was saying, we are just coordinating via Government agencies the Federal family, as they would put it.

Senator WHITEHOUSE. But there is nothing that you are aware of in the process that limits them to that? I mean, if the worst case scenario is that a polluter comes to the White House, makes big campaign contributions, agrees to be a pioneer or whatever it is, and says that they are going to, you know, but they want OMB to put the word in for them through this process, there is nothing in the process itself that would ever disclose that or surface that or prevent that from happening.

Mr. STEPHENSON. We have no evidence of that happening. All we are saying is that to have complete transparency in the process eliminates——

Senator WHITEHOUSE. I am not suggesting it has happened, either. But there is nothing about this process that would prevent that or disclose it if it happened at this point.

Mr. STEPHENSON. That is our fear.

Senator WHITEHOUSE. Yes. Thank you.

Senator BOXER. Thanks, Senator.

Let me say that, to Senator Craig, who said this hearing is just concerned about process and not outcomes, that is wrong. The outcomes have already been a disaster, because they put this into play without it being officially done. They have already put this process into play.

And what has happened is, EPA itself said they should be doing 100 chemicals, regulating over 100 in 2 years, and they have regulated 4 chemicals. So outcome, yes. We are not seeing the protection of the American people.

Second, I want to thank GAO from the bottom of my heart for doing this for us. This notion that secrecy is going to be built into this process, where the American people are the ones who will suffer if the wrong decision is made is a complete outrage. It goes against the spirit of this whole Country, which is openness and trusting its citizens with information.

Third, shunting scientists aside and putting in front the political folks is so obviously a problem that I can't believe we are not hearing outcries from my friends on the other side of the aisle who, when and if we do get a Democratic President, it will be those folks in the room. No one should be in that room in the early risk assessment stages at all except the scientists and the people concerned about health. Mr. Stephenson, if you made any point in a passionate way, that is the point.

There is room for all these other folks as we debate what to do. But in the setting of what is safe for our people, it has to be pure, done by the people who have no axe to grind, who simply have a concern with the science and what it means to the health and safety of our people.

Look, when I go home I hear all the time the fears of my constituents about what their kids are being exposed to, what their pregnant daughters are being exposed to, what should she eat, what should she avoid, what is the problem? I wish I could tell them that we have had a stellar, we have done a stellar job here. We haven't. It is a nightmare.

And I will tell you, it is already a nightmare. If this process is put into place, it will institutionalize this nightmare and set us up for scandal. Because Senator Whitehouse said it as clearly as it needed to be said, people are going to be represented around that table, and we will never know. And Senator Whitehouse, I want you to know, as we struggle to get e-mails back and forth on the waiver, we can't get them. And you know what the answer is from the Bush White House? You are not entitled to these, they are interagency comments.

So you know, we weren't born yesterday. Well, you can tell that from looking at me, I was definitely not born yesterday and I do

understand that this is a secret process, it is a nightmare. And I just want to thank our witnesses for making it very clear to us that is the case. Thank you very much.

We will call up our second and final panel. Professor Linda Giudice, who is an M.D., a Ph.D., a Chair of Obstetrics, Gynecology and Reproductive Sciences at the University of California, San Francisco; Annette Gellert, who is the Co-Founder and Chair of the WELL Network; V.M. DeLisi, Fanwood Chemical, Inc., Synthetic Organic Chemicals Manufacturing Association; Laura Plunkett, Ph.D., Integrative Biostrategies, LLC, minority witness; Professor Lynn Goldman, she is our pediatrician, Chair of the Program in Applied Public Health, Johns Hopkins University, former Clinton EPA Assistant Administrator for Pesticides and Toxic Substances.

Well, those were such long introductions you have time to actually have a seat. So we will go forward, and we will ask Dr. Giudice to address us on this. We will give you each 5 minutes and then we will have lots of time for questions.

STATEMENT OF LINDA C. GIUDICE, M.D., PH.D., MSC., PROFESSOR AND CHAIR, DEPARTMENT OF OBSTETRICS, GYNECOLOGY AND REPRODUCTIVE SCIENCES, UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Dr. GIUDICE. Thank you. Good morning, Chairman Boxer and Committee members. Thank you for the opportunity to provide testimony at this important hearing today, where I shall focus on three things: one, disturbing trends about male and female reproductive health and development; two, how chemicals in our environment can affect these; and three, preserving health now and for future generations.

During my career as a reproductive endocrinologist and infertility specialist, I have treated thousands of patients with infertility and reproductive disorders: young men with abnormal sperm, teens into menopause, little girls with puberty at 6 years old and women with endometriosis, uterine fibroids, incapacitating pain, infertility and miscarriage. We do not know the underlying causes for most of these disorders, but increasing scientific evidence suggests that environmental contaminants play a role.

Five years ago, one of my patients questioned whether her exposure to environmental chemicals as a child growing up near a PCB-contaminated site on the East Coast could play a role in her infertility. For me, this was a wake-up call, because we know that hormones can affect human development and some environmental chemicals at like hormones.

There are disturbing trends in the United States. The percentage of women in their peak time of fertility, less than 25 years of age, who report difficulty in conceiving and maintaining pregnancy, has doubled from 4.3 to 8.3 percent between 1982 to 2002. Over the past 50 years, sperm counts have decreased by 50 percent in industrialized regions. Compared to 30 years ago, over 25 percent more women get breast cancer, 45 percent more men get testicular cancer and 76 percent get proState cancer. Thirty percent more babies are born prematurely, and among the most common birth defects today are malformations of the male reproductive system.

Scientific evidence highly suggests that exposures in the womb or in early childhood to environmental contaminants can cause in humans some of these trends, including birth defects, pre-term birth, low birth weight, learning disabilities, childhood cancers and later effects as adults, diabetes, obesity, heart disease, infertility and cancer. So adult disorders happening because of exposures in utero.

Since World War II, nearly 90,000 chemicals have been produced and there is ubiquitous exposure to environmental contaminants in our air, water, food, drink, cosmetics, personal care products, pesticides and everyday household products. Exposure to these around the time of conception, during pregnancy or infancy can be particularly powerful because these are times of special vulnerability, where important developmental changes are taking place. These exposures can also affect subsequent generations.

For example, bisphenol A, a chemical that is in can linings and present in nearly every one in the U.S., can have such an effect. Dr. Pat Hunt at Washington State showed that female fetuses of BPA-exposed pregnant mice had damaged eggs and abnormal chromosomes. Abnormal chromosomes are a leading cause of miscarriage, congenital defects and mental retardation in humans. The study also showed the prenatal BPA exposure resulted in damage across generations.

Another example is phthalates, common in personal care and vinyl products. Exposure during pregnancy can lower fetal testosterone, a hormone important for male reproductive tract development. In animals, this is linked to undescended testicles and deformed penis at birth. Dr. Shanna Swan has shown that pregnant women with higher phthalates have a greater risk of having little boys with decreased genital dimensions, supporting effects on the male system in the human.

Exposure to chemicals like these interferes with proper functioning of the endocrine system, raising concern among health care providers and scientists, and others include pesticides, solvents and heavy metals. So what to do?

We need to ensure that couples can conceive if they wish and have a healthy pregnancy and healthy children and grandchildren. We need the Federal Government to fulfill its mission, assemble existing scientific knowledge, impartially reviewing it in an unbiased manner following scientific principles free of ideology. For some chemicals we have scientific data, but for many, we do not. And the absence of data doesn't mean that a chemical is safe, it just means that we have no data.

For these chemicals, we need actions that require providing sufficient information so our Government can move forward to prevent harmful exposure and by acting now, to guarantee the health of our children and our grandchildren and generations to come.

My thanks go to the Society for Women's Health Research, our UCSF Program on Reproductive Health and the Environment, the Reproductive Health Technologies Project, and the American Society for Reproductive Medicine, for their help in preparing this testimony. Thank you.

[The prepared statement of Dr. Giudice follows:]

Testimony of Linda C. Giudice, MD, PhD, MSc
U.S. Senate Committee on Environment and Public Works
on
"Oversight on EPA Toxic Chemical Policies"
Tuesday, April 29, 2008
Dirksen Senate Office Building, Washington DC

Senator Barbara Boxer, Chairman
Senator James M. Inhofe, Ranking Member

Good Morning, Chairman Boxer, Senator Inhofe, committee members, and guests. I am Dr. Linda Giudice, Professor and Chair of the Department of Obstetrics, Gynecology, and Reproductive Sciences at the University of California, San Francisco. Thank you for the opportunity to testify at this important hearing. Today I shall focus on three things:

1. Disturbing trends about male and female reproductive health and development.
2. How chemicals in our environment can affect reproductive and developmental health and the relationship to developing adult diseases.
3. What we can do to preserve our health and that of future generations.

First, before I begin about trends I'd like to share some experiences during my career as a reproductive endocrinologist and infertility specialist. I have treated thousands of patients with infertility and other reproductive disorders – young men with very abnormal sperm or with a history of testicular cancer; young women, some of them as young as 17, already in menopause; little girls with onset of puberty at 6 or 8 yrs old; and women with estrogen-dependent disorders, like endometriosis and uterine fibroids that can result in incapacitating pain, lead to compromised fertility and increased risk of miscarriage. For the most part, we do not know the underlying causes of these disorders, but there is increasing evidence that environmental contaminants play a role. Some causes are genetic, but most are not. Couples and individuals struggle with an inability to conceive, with cancer, with debilitating pain, or having an abnormal baby - challenges that most of us would find hard to face, and which are more common than you may think.

About 5 years ago, one of my infertility patients questioned whether her exposure to environmental chemicals as a child growing up near a PCB contaminated waste site on the east coast could play a role in her inability to conceive a child. For me this was a wake up call, because we know that hormones affect human development and that some environmental chemicals act like hormones. Since then, reproductive science has exploded with data about environmental chemicals and how they affect reproduction and adult diseases due to exposures in utero.

Trends. There are disturbing trends in the United States [1].

- More young women under the age of 25, their time of peak fertility, are reporting difficulty conceiving and maintaining their pregnancies. In a national survey conducted by the National Center for Health Statistics [2], between 1982 and 2002 the percent of women reporting difficulty in conceiving and maintaining pregnancy doubled from 4.3% to 8.3%.
- Sperm counts have decreased by 50% during the past 50 years in several industrialized regions.
- Compared to 30 years ago, over 25% more women get breast cancer, over 45% more men get testicular cancer, and 76% more men get prostate cancer.
- Thirty percent more babies are born premature, and on average babies are born one week earlier now than they were 15 years ago.
- Some of the most common birth defects today are malformations of the male reproductive system.

We also have increasing scientific evidence of the impact that exposures in the womb or during early childhood to environmental contaminants can have on human health. [3]. Some effects can occur immediately, such as birth defects, pre-term birth, and low birth-weight. Some effects can occur during childhood, such as learning disabilities and childhood cancers, and some effects do not occur until adulthood, such as diabetes, cardiovascular disease, and cancers. Exposures in the womb can also affect subsequent fertility as an adult [1] .

Chemical Exposures – when, where, and how: Since World War II, chemical production in the U.S. has increased more than twenty-fold, while since 1979 the number of chemicals registered for commercial use has grown by over 30%.. There is ubiquitous exposure to environmental contaminants through air, water, food and drink, cosmetics, personal care products, pesticides and herbicides, and everyday household items.

Exposure to chemical contaminants that occurs around the time of conception, during pregnancy, or during infancy can be particularly powerful. These are critical times of development, or "periods of vulnerability," during which unique and important developmental changes are taking place. Chemical exposures during these periods can interfere with these processes and result in negative health effects to the child or even the grandchildren.

An example of this is exposure to Bisphenol A, also known as BPA. Recent government data show that almost every person in the U.S. is exposed to BPA. BPA is found in many places including polycarbonate plastic and can linings. Studies have found that exposure during early life, during critical windows of development, can result in permanent alterations to a number of reproductive systems in the body, increasing the risk of future reproductive health problems. In a series of important studies by Dr. Pat Hunt at Washington State University, pregnant mice were exposed to BPA, which resulted in exposure to the developing fetus. This exposure to BPA damaged female

fetus's new eggs, known as oocytes. The daughter's eggs were more likely to have chromosomal abnormalities, which increased the likelihood of a granddaughter with genetic defects. Chromosomal abnormalities are the leading cause of miscarriage, congenital defects and mental retardation in humans. Dr. Hunt's studies revealed that prenatal exposure to BPA resulted in damage passed from the mother to the daughter, to the granddaughter, passing down two generations.

Another example is exposure to phthalates. People are exposed to phthalates from numerous sources, including personal care and vinyl products. Phthalates can interfere with production of testosterone, and exposure to phthalates during pregnancy can result in decreased levels of testosterone in the fetus. The male fetus must have a certain level of testosterone in order for the development of the male reproductive tract, and exposure to phthalates in animals has been linked to reproductive effects in male babies, like undescended testicles and deformities of the penis. Data of Dr. Shanna Swan of the University of Rochester show pregnant women with higher phthalates were more likely to have little boys with decreased genital dimensions, which indicate effects on the male reproductive system.

Exposure to these chemicals, phthalates and Bisphenol A, which have the ability to interfere with the proper functioning of the endocrine system, are just two examples that are raising concern among health care providers and scientists. Others, including pesticides, solvents, and heavy metals, also have been shown to have similar effects.

To address these very real concerns about the impact of environmental contaminants on reproductive health, UCSF has launched the Program on Reproductive Health and the Environment (PRHE). PRHE is dedicated to advancing scientific inquiry, professional training, citizen education, and health policies that reduce the impacts of environmental contaminants on reproductive and developmental health.

What to do. We need to ensure that couples can conceive if they wish, have a healthy pregnancy, a health child, and ultimately a healthy grandchild. However, to do this we need the Federal government to fulfill its mission. For many chemicals, we have sufficient scientific information to act. This requires assembling the existing scientific knowledge, reviewing it in an impartial and unbiased manner, following scientific principles free of ideology, so that we can begin to move forward and allow the decisions to be made to prevent exposures that can result in harm.

But there are many chemicals where we have no scientific data. The absence of scientific data does not mean the chemical is safe, it only means that that we have a lack of data. For these chemicals we need actions that require providing sufficient information so the government can move forward to prevent harmful exposures. By acting now, we can improve our health and that of our children and our grandchildren, and the health of generations to come

Thank you

References

1. Woodruff, T.J., A. Carlson, J.M. Schwartz, and L.C. Giudice, *Proceedings of the Summit on Environmental Challenges to Reproductive Health and Fertility: executive summary.* Fertil Steril, 2008. **89**(2 Suppl): p. e1-e20.
2. Chandra, A., G. Martinez, W. Mosher, J. Abma, and J. Jones, *Fertility, family planning, and reproductive health of U.S. women: Data from the 2002 National Survey of Family Growth*, N.C.f.H. Statistics, Editor. 2005, Vital Health Stat.
3. Janssen, S., V. Fujimoto, and L.C. Giudice, *Endocrine Disruption and Reproductive Outcomes in Women*, in *Endocrine-Disrupting Chemicals: From Basic Research to Clinical Practice*, A. Gore, Editor. 2007, Humana Press: Totawa, NJ. p. 203-223.

Other Materials for the Record

PRHE Fact Sheet

Executive Summary: Proceedings of the Summit on Environmental Challenges to Reproductive Health and Fertility.

University of California, San Francisco
Program for Reproductive Health and the Environment

Protecting our Reproductive Health and Fertility. Latest Findings on Environment Impacts

In the US today, there is increasing concern about the impacts of environmental contaminants on the reproductive health and fertility of women, men, and families.

In women

- At least 12% of women report difficulty in conceiving and maintaining pregnancy. This appears to be increasing, most markedly in women under 25 years old.
- Other fertility-related diseases, like endometriosis and polycystic ovarian syndrome, are diagnosed more frequently now, which may result from an increase in prevalence, better detection, or both.

In men

- Testicular cancer has been increasing the US since the 1970s, with a reported 60% increase among whites and Asians and 40% increase in blacks.

In their children

- Hypospadias (deformities of the penis in infants), cryptorchidism (undescended testicles in babies) and testicular cancer are increasing while sperm count and testosterone levels are declining in certain populations.

What the New Research Tells Us

- US Centers for Disease Control and Prevention data show exposures to chemicals like **phthalates**, **bisphenol A**, and **perfluorinated compounds** are common and almost everyone has contaminants in their bodies - some even at levels near or above those shown in scientific studies to cause adverse effects on reproductive health.
- Exposures to chemical contaminants around the time of conception, during pregnancy or during infancy are particularly powerful because of vulnerability during development.
- During this time, exposures to **bisphenol A** found in polycarbonate plastic and can linings can cause permanent changes and increased risks of later reproductive health problems (infertility, miscarriage, breast cancer, prostate cancer).

  Prenatal exposure to **phthalates** found in personal care products and vinyl products has been linked to reproductive effects in male babies, like undescended testicles and deformities of the penis.

  Cadmium, a metal found in cigarette smoke and in the air, has been linked to gynecological disorders in women, such as endometriosis, and reduced sperm motility.

  Prenatal exposures in animals to **perfluorinated chemicals**, common in stainproof and stick-free products, can result in irreversible damage in offspring.
- Health effects can be passed from one generation to the next, effecting the children and grand children of exposed mothers and fathers.
- A wide range of wildlife populations have been adversely affected by exposure to endocrine-disrupting contaminants.

  Impacts among birds, fish, shellfish, mammals and reptiles include decreased fertility and increased reproductive tract abnormalities; feminization and demasculinization in the males; and masculinization and defeminization in the females.

UC San Francisco's new Program on Reproductive Health and the Environment

The compelling nature of the collective science, with observations in humans, animal models, and wildlife, raises concern for future health of individuals and families in the U.S. To address these concerns, UCSF has launched the Program on Reproductive Health and the Environment (PRHE). PRHE is dedicated to advancing scientific inquiry, professional training, citizen education, and health policies that reduce the impacts of environmental contaminants on reproductive and developmental health.

What PRHE has done and is doing

- **Summit on Environmental Challenges to Reproductive Health and Fertility Impacts:** In early 2007, a ground breaking gathering of over 400 scientists, clinicians, health-effect and community groups, and policy-makers, discussed current science and steps to move forward to protect the health of our families. This Summit on Environmental Challenges to Reproductive Health and Fertility was organized with the **Collaborative on Health and Environment (CHE)**.
- **Developing a Reproductive Health Toolkit:** Working with researchers, health care providers and health-effected groups we will be developing materials to advice patients about the importance of avoiding environmental exposures during conception and pregnancy.
- **Researching** the impacts of environmental contaminants on reproductive and child health.
- **Assessing the most effect policies** that incorporate the new science into improved public policies.

UCSF Program for Reproductive Health and the Environment
http://www.ucsf.edu/coe/prhe.html

SPECIAL CONTRIBUTION

Proceedings of the *Summit on Environmental Challenges to Reproductive Health and Fertility*: executive summary

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The 2007 *Summit on Environmental Challenges to Reproductive Health and Fertility* convened scientists, health care professionals, community groups, political representatives, and the media to hear presentations on the impact of environmental contaminants on reproductive health and fertility, and to discuss opportunities to improve health through research, education, communication, and policy. Environmental reproductive health focuses on exposures to environmental contaminants, particularly during critical periods of development, and their potential effects on future reproductive health, including conception, fertility, pregnancy, adolescent development, and adult health. Approximately 87,000 chemical substances are registered for commercial use in the United States, with ubiquitous human exposures to environmental contaminants in air, water, food, and consumer products. Exposures during critical windows of susceptibility may result in adverse effects with lifelong and even intergenerational health impacts. Effects can include impaired development and function of the reproductive tract and permanently altered gene expression, leading to metabolic and hormonal disorders, reduced fertility and fecundity, and illnesses such as testicular, prostate, uterine, and cervical cancers later in life. This executive summary reviews effects of pre- and postnatal exposures on male and female reproductive health, and provides a series of recommendations for advancing the field in the areas of research, policy, health care, and community action. (Fertil Steril® 2008;89:281–300. ©2008 by American Society for Reproductive Medicine.)

Key Words: Environmental contaminants, reproductive health, endocrine disrupting chemicals, fertility, fecundity, hormone disruption, sperm quality, reproductive tract development

On January 28–30, 2007, the *Summit on Environmental Challenges to Reproductive Health and Fertility* was convened at the Mission Bay Campus of the University of California, San Francisco (UCSF). The *Summit* was the product of a collaboration between the UCSF Program on Reproductive Health and the Environment in the Department of Obstetrics, Gynecology and Reproductive Sciences, the UCSF National Center of Excellence in Women's Health, and the Collaborative on Health and the Environment. This unique gathering coalesced the field of environmental reproductive health by bringing together over 400 scientists, researchers, health care professionals, trainees, health-affected groups, community and political representatives, and the media to discuss what is currently known about the impacts of environmental contaminants on reproductive health and fertility. The compelling nature of the collective science, with observations in humans, animal models, and wildlife, raised concern for the future health of individuals and families. The Summit also set the stage to improve health through research, education, communication, and changes in public health policy. This executive summary presents the highlights from the accompanying *Supplement on Environmental Challenges to Reproductive Health and the Environment* (1), which summarizes the state of the science presented at the *Summit*, and outlines the key "next steps" *Summit* participants recommended for research, policy, health care, community action, and safe work.

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DEFINING THE FIELD

Environmental reproductive health focuses on exposures to environmental contaminants (synthetic chemicals and metals), particularly during critical periods of development (such as before conception and during pregnancy), and their potential effects on all aspects of future reproductive health throughout

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the life course, including conception, fertility, pregnancy, child and adolescent development, and adult health (Fig. 1).

ENVIRONMENTAL CONTAMINANTS

Since World War II, there has been a dramatic increase in human exposures to both natural and synthetic chemicals. As of 2006, there are approximately 87,000 chemical substances registered for commerce in the United States (US) (2). Common environmental pollutants include pesticides and herbicides such as atrazine and chlorpyrifos; volatile organic compounds such as benzene, toluene, and chloroform; heavy metals such as lead, mercury, and arsenic; air contaminants such as carbon monoxide, ozone, particulate matter, and environmental tobacco smoke (ETS); and persistent organic pollutants, such as the dioxins, polychlorinated biphenols (PCBs), the pesticide dichlorodiphenyltrichloroethane (DDT), and its breakdown product dichlorodiphenyldichloroethylene (DDE).

Although many environmental contaminants can affect reproductive health (Table 1), there is an important class of chemicals called endocrine disrupting chemicals (EDCs) that interfere with the production, release, transport, metabolism, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis and the regulation of developmental processes. Some of the common EDCs discussed at the *Summit* include bisphenol A (BPA), phthalates, and certain pesticides (e.g., vinclozolin, dicofol, atrazine). Many of these compounds alter estrogen, androgen, and thyroid signaling, which are essential for normal embryonic development and reproductive activity in all vertebrates studied to date (3–5). They can also alter hormone synthesis, storage on plasma proteins, and hepatic biotransformation and clearance (6); disrupt neural and immune signaling pathways (7–9); and alter the regulation of gene expression (e.g., DNA methylation, RNA stability, protein degradation) [reviewed by (10)]. In some cases, altered DNA methylation patterns have been shown to be heritable (11, 12).

Studying the effects of EDCs on the reproductive system is a natural area of inquiry, as EDCs can interact with the hormonal system, which regulates development and maintenance of the reproductive system. However, because EDCs also target the neuroendocrine system, which plays regulatory and homeostasis roles in the control of human physiology, exposure to EDCs has broader implications for health.

EXPOSURE TO MULTIPLE CHEMICALS

Humans are exposed daily to a mixture of environmental contaminants in air, water, and food. In a recent biomonitoring study of over 150 contaminants, the US Centers for Disease Control and Prevention reported that all 150 chemicals were detected in some portion of the US population, and that several of the chemicals, such as environmental tobacco smoke, lead, mercury, and phthalates, are detected in nearly all of the population (13). These and similar biomonitoring efforts improve our understanding of current body burdens of environmental contaminants. With this knowledge comes a need for better science on the health risks associated with current patterns of exposure, including increased risks resulting from exposures to multiple chemicals. For example, most studies and regulatory focus have been on exposures to individual phthalates, which may underestimate the actual risks, as recent studies have found that simultaneous prenatal exposure to both di(*n*-butyl) phthalate (DBP) and di(2-ethylhexyl) phthalate produced reproductive malformations in the offspring in a cumulative, dose-additive manner (14). Finally, biomonitoring data indicate that more effort is needed toward approaches that identify and mitigate exposure to harmful chemicals before measuring harmful contaminants in people.

SUSCEPTIBLE POPULATIONS

Environmental chemicals can cause a broad spectrum of effects, which depend not only on route of exposure and dose, but on the susceptibility of the individual to the compound. Age, gender, and genotype can influence susceptibility to disorders, anatomic abnormalities, and diseases from

FIGURE 1

Key definitions for environmental reproductive health.

Environmental Reproductive Health: Interdisciplinary study of exposures to environmental contaminants, particularly during critical periods in development (such as before conception and during pregnancy), and their potential effects on all aspects of future reproductive health throughout the life course, including conception, fertility, pregnancy, child and adolescent development, and adult health.

Environmental Contaminants: synthetic chemicals and metals in our environment, including air, water, soil, food, consumer products, and the workplace.

Reproductive Health: Ability to conceive, to carry a pregnancy, pregnancy quality and outcomes, pubertal effects, and adult reproductive health disorders.

Woodruff. Environmental reproductive health. Fertil Steril 2008.

TABLE 1

Environmental contaminants: sources and selected health effects from developmental and adult exposures (animal and human data). (Adapted from *Challenged Conceptions*, Collaborative on Health and the Environment, 2005 [254]).

Contaminant	Sources	Examples of health effects associated with exposure during adulthood	Examples of health effects associated with exposure during development
Air Pollution	Common air pollutants include carbon monoxide, lead, ground-level ozone, particulate matter, nitrogen dioxide, and sulfur dioxide. Air pollution arises from a variety of sources, including motor vehicles, industrial production, energy (coal) production, wood burning, and small local sources such as dry cleaners.	fetal loss[d] (254)	low birth weight (254) preterm delivery (254)
Bisphenol A (BPA)	Industrial chemical and building block for polycarbonate plastic and epoxy resins. Found in the lining of metal food and drink cans, plastic baby bottles, pacifiers and baby toys, dental sealants, computers, cell phones, hard plastic water bottles, paints, adhesives, enamels, varnishes, CDs and DVDs, and certain microwavable or reusable food and drink containers.	oocyte chromosome abnormalities (162) recurrent miscarriage (160) decreased semen quality (180, 181)	altered puberty onset (182) obesity (182) altered prostate development (183, 184) decreased semen quality (181, 185) hormonal changes (185)
Disinfection by-products	Over 600 compounds formed by the reaction of chemical disinfectants (most often chlorine) with natural organic matter, primarily in surface waters. Most prevalent compounds are trihalomethanes.	menstrual irregularities[c] (131, 186)	fetal growth, IUGR (177–179)
Ethylene oxide	Chemical sterilant used in dental and medical practices.	fetal loss[d] (187, 188) decreased semen quality[a] (188) miscarriage in female partner (188)	
Glycol ethers	Used in paints, varnishes, thinners, printing inks, electronics, semi-conductor industry, leather, photographic film, varnish, enamels, cosmetics, perfumes, brake fluids, wood stains.	longer menstrual cycles (135) decreased semen quality[a] (100, 189) reduced fertility[b] (190, 191) fetal loss[d] (189, 190)	

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TABLE 1

Continued.

Contaminant	Sources	Examples of health effects associated with exposure during adulthood	Examples of health effects associated with exposure during development
Pesticides	Broad category that includes many classes of insecticides, fungicides, herbicides, rodenticides, and furnigants. Pesticides are used on food, in residential and industrial settings. Exposures can occur through food, drinking water, or from home use.	menstrual irregularities[c] (133, 166) reduced fertility[b] (147, 148, 188, 192) decreased semen quality[a] (189, 193–195) miscarriage in female partner (151, 153, 196, 197) sperm chromosome abnormalities (198, 199) hormonal changes (100, 193, 200)	altered sex ratio (H,A) (100, 201) altered puberty onset (202–204) malformations of reproductive tract[d] (205–207) reduced fertility (193, 208) fetal growth, IUGR (209–211)
Phthalates	Plasticizers added to soften plastics like PVC; also found in cosmetics, perfumes, toys, pharmaceuticals, medical devices, lubricants and wood finishers.	altered (earlier) menarche onset (127) estrous cycle, ovulatory irregularities (187) decreased semen quality[a] (212) reduced fertility[b] (213) fetal loss[d] (187) endometriosis (141, 142)	shortened anogenital distance (214) malformations of reproductive tract (215) hormonal changes (215) decreased semen quality[a] (215)
Solvents	Benzene, toluene, xylene, styrene, 1-bromopropane, 2-bromopropane, perchloroethylene, trichloroethylene, and others. Solvents include some of the top production volume chemicals in the US Used in plastics, resins, and nylon, synthetic fibers, rubbers, lubricants, dyes, detergents, drugs, pesticides, glues, paints, paint thinners, fingernail polish, lacquers, detergents, printing and leather tanning processes, insulation, fiberglass, food containers, carpet backing, cleaning products, and a component of cigarette smoke. Exposure is primarily through breathing contaminated air.	hormonal changes(100, 187, 216) menstrual irregularities[c] (187, 188, 193) decreased semen quality[a] (100, 188, 217, 218) reduced fertility[b] (188, 218–222) fetal loss[d] (187, 188, 193, 223) miscarriage in female partner (188)	
Cigarette smoke	Includes active and/or passive smoking	hormonal changes (219, 224) decreased semen quality[a] (219) reduced fertility[b] (188, 219) miscarriage (219) early menopause (219)	IUGR (225) Low birth weight (225) Preterm delivery (225) decreased semen quality[a] (124, 226)

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TABLE 1

Continued.

Contaminant	Sources	Examples of health effects associated with exposure during adulthood	Examples of health effects associated with exposure during development
Pharmaceuticals	Examples: DES, ethynylestradiol (birth control pill)		malformations of reproductive tract[d] (227, 228) altered hormone response (228) menstrual irregularities[c] (H, A) (187, 227) reduced fertility[b] (H, A) (187, 227) uterine fibroids (227) miscarriage (187)
Perfluorinated compounds (PFOS, PFOA)	Used to make fabrics and carpets stain-resistant and water-repellant; in coating of cooking pans, floor polish, insecticides, food wrap coatings. Accumulate in the environment and the food chain.		hormonal changes (229) reduced birth weight (230) fetal loss (230, 231)
Polybrominated Diphenyl Ethers (PBDEs)	Flame retardants found in furniture foam, mattresses, textiles, computers and electronics. Accumulate in the food chain.		decreased semen quality[a] (232)
Octylphenol, Nonylphenol	Used to make surfactants (detergents), pesticides, paints, and other formulated products, and also as plasticizers and UV stabilizers in plastics. Primary exposure is from drinking water contaminated by sewage and wet-weather runoff.		hormonal changes (227) altered puberty onset (233) hormonal changes (185, 234) decreased semen quality[a] (A) (185, 235) decreased testes size (234, 235)
Chlorinated Hydrocarbons			
Dioxins/Furans	Byproducts of the manufacture and burning of products that contain chlorine.	menstrual irregularities[c] (132, 134, 137, 140, 166, 187, 236)	malformations of the reproductive tract[d] (236, 243–245)
Polychlorinated biphenols (PCBs)	Industrial insulators and lubricants. Banned in the US in 1976. Persist for decades in the environment. Accumulate up the food chain.	hormonal changes (138–140, 187, 193, 236) reduced fertility[b] (187, 236) endometriosis (187, 237, 238)	altered estrous cycle (227) reduced fertility[b] (227) altered sex ratio (100, 186, 187, 236, 246)
Organochlorine pesticides	Class of pesticides used largely as insecticides. (ex: DDT, chlordane, HCB.) Largely banned in the US Persist for decades in the environment. Accumulate up the food chain.	fetal loss[d] (144, 236, 239) decreased semen quality[a] (236, 239, 240) altered puberty onset (127, 129, 241) altered menarche onset (126, 128, 241, 242)	altered puberty onset (126, 241) decreased semen quality[a] (91, 243) delayed time to pregnancy (247)
Pentachlorophenol	Wood preservative for utility poles, railroad ties, and wharf pillings. Formerly used as a pesticide.		

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TABLE 1

Continued.

Contaminant	Sources	Examples of health effects associated with exposure during adulthood	Examples of health effects associated with exposure during development
Metals			
Lead	Used in batteries, ammunition, metal products, X-ray shields. Reduced use in gasoline, paints, ceramic products, caulking, and pipe solder. Most common source of exposure in the US is lead-based paint in older homes, lead-contaminated house dust and soil and vinyl products.	fetal loss[d] (187, 217, 248) reduced fertility[b] (100, 187, 193, 217, 249, 250) hormonal changes (100, 187, 193, 251) menstrual irregularities[c] (130, 187) abnormal sperm (94, 100, 252) altered puberty onset (124–126)	hormonal changes (227) altered puberty onset (84, 126)
Mercury	Used in thermometers, dental fillings, batteries, vaccines and other industries. Air and water contaminated by industrial emissions and the combustion of coal and waste. Accumulates in food chain; most common source of exposure in US is contaminated seafood.		
Manganese	Used in the production of batteries, in dietary supplements, and as ingredients in some ceramics, pesticides, and fertilizers. Gasoline additive.		
Cadmium	Used in industry and consumer products, mainly batteries, pigments, metal coatings, plastics, and some metal alloys.		

Note: IUGR = intrauterine growth retardation; DDT = dichlorodiphenyltrichloroethane; DES = diethylstilbestrol; HCB = hexachlorobenzene.

[a] Decreased semen quality could include low semen, abnormal sperm shapes or motility, decreased sperm counts.

[b] Reduced fertility could include both infertility and increased time to pregnancy (reduced fecundity).

[c] Menstrual irregularities could include short or long menstrual cycles, missed periods, abnormal bleeding, anovulaion.

[d] Malformations of the reproductive tract in males, could include shortened ano-genital distance in animals or hypospadias (humans), undescended testicles (cryptorchidism), small testicles (hypoplasia), and structural abnormalities of the epididymis. In females, could include small ovaries, reduced number of follicles (eggs), and structural abnormalities of the oviducts, uterus, cervix, and/or vagina.

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exposures. For example, we know that children are not small adults; they have different behaviors, metabolism, and responses to infectious and environmental challenges. The elderly may also be a population at special risk to environmental chemicals.

CRITICAL AND SENSITIVE WINDOWS OF SUSCEPTIBILITY

A *critical window of susceptibility* is a time-sensitive interval during development when exposures to environmental contaminants can disrupt or interfere with the physiology of a cell, tissue, or organ (15, 16). It is a period characterized by marked cellular proliferation and development and numerous changing metabolic capabilities in the developing organism (16, 17). Exposures to environmental contaminants during this window may result in adverse, permanent, and irreversible effects that can have lifelong and even intergenerational impacts on health.

Researchers have suggested the need to also define *sensitive windows of susceptibility*. Exposures during sensitive windows of susceptibility may still affect development or result in eventual adult disease, but with reduced magnitude compared with the effect of exposure during the critical window of susceptibility (16, 18). For example, diethylstilbestrol (DES) exposure reprograms the expression of estrogen responsive genes in Eker rats exposed on postnatal days 3–5 or 10–12 (critical window of susceptibility), leading to increased incidence of uterine leiomyoma. In contrast, rats exposed on postnatal days 17–19 (sensitive window of susceptibility) did not experience this developmental programming, and had a rate of uterine leiomyoma that was elevated but not statistically different from control animals (19).

Given that development continues after birth, critical and sensitive windows occur periconceptually (before, during, and shortly after the fertilization of the egg) and during pregnancy, infancy, childhood, and puberty (Fig. 2).

DEVELOPMENTAL PROGRAMMING AND FETAL ORIGINS OF ADULT DISEASE

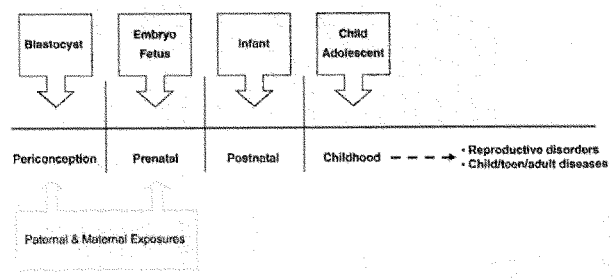
Studies from the 1990s found that adverse effects on the fetal environment, such as poor maternal nutrition, can result in an increased risk of adult onset of chronic conditions such as coronary heart disease (20–22). These findings led to the fetal origins of disease hypothesis (commonly known as the "Barker Hypothesis"), which proposes that exposures to adverse insults during critical or sensitive windows of development can permanently reprogram normal physiologic responses, and thus give rise to illnesses and metabolic and hormonal disorders later in life (23–28).

The DES Example

Prenatal exposure to DES, a synthetic estrogen and an EDC, provides an unfortunate example of developmental programming. DES was given to pregnant women in the US between 1938 and 1971 under the erroneous assumption that it would prevent pregnancy complications. In fact, in utero exposure to DES alters the normal programming of gene families, such as Hox and Wnt, which play important roles in reproductive tract differentiation (28–31). As a result, female offspring exposed to DES in utero are at increased risk of clear cell adenocarcinoma of the vagina and cervix, structural reproductive tract anomalies, infertility, and poor pregnancy outcomes, whereas male offspring have an increased incidence of genital abnormalities and a possibly increased risk of prostate and testicular cancer (32). These observed human effects have been confirmed in numerous animal models, which have also provided information on the toxic mechanisms of DES. Animal experiments have also predicted changes later found in DES-exposed humans, such as oviductal malformations (33), increased incidence of uterine fibroids (34–36), and second-generational effects (37, 38) such as increased menstrual irregularities (39) and possibly ovarian cancer (40) in

FIGURE 2

Windows of susceptibility to environmental insults [adapted from (253)].



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DES granddaughters and increased hypospadias in DES grandsons (41, 42).

DES is but one example of how exposure to EDCs can disrupt developing organ systems and cause abnormalities, many of which appear only much later in life or in the subsequent generation (43), such as endometriosis, fibroids, and breast, cervical, and uterine cancer in women; poor sperm quality and increased incidence of cryptorchidism and hypospadias in men; and subfertility and infertility in men and women (28).

SIGNALS FROM WILDLIFE

For over a century, wildlife and laboratory animals have been used to predict the human health effects of various environmental contaminants. Although each species has its unique attributes, a growing literature indicates that substantial conservation exists in the underlying molecular, cellular, and physiologic systems associated with vertebrate reproduction (44). For example, estrogen, androgen, and thyroid signaling are essential for normal embryonic development and reproductive activity in all vertebrates studied to date (3–5). Furthermore, wildlife studies demonstrate the effects of levels and mixtures of exposures in our environment in genetically diverse populations (44). Therefore observations from wildlife are directly relevant to assessing potential environmental influences on human reproduction.

In the early 1990s, studies began to associate environmental contamination with altered reproductive performance in wild populations of fish, amphibians, reptiles, and birds (45). For example, studies in fish demonstrate increased rates of feminized male phenotype and reduced fertility from environmental exposures to ethynylestradiol, a synthetic estrogen found in birth control pills and increasingly in treated sewage effluent; tributyltin, an antifouling agent used on boats; BPA; tetrabromobisphenol A, a widely used flame retardant; and nitrate, a common fertilizer (44). Studies in alligators inhabiting pesticide-contaminated lakes report reduced fertility and increased occurrence of multioocyte follicles (ovarian follicles with multiple rather than the normal single oocyte) (46); alterations in folliculogenesis resulting in multioocyte follicles have been associated with infertility and early embryonic loss in DES-treated mice (47, 48). Exposure of reptilian embryos to endogenous (estradiol-17β), pharmaceutical (e.g., ethynylestradiol, DES), or industrial (e.g., DDT, DDE, BPA, trans-nonachlor) estrogens during a critical window of susceptibility during development induces sex reversal at male incubation temperatures, leading to increased female sex ratios (49–52). In addition, exposure to even lower concentrations of these contaminants alters steroidogenesis in the ovary or testis in neonates and juveniles (53). Fish and amphibians also experience effects following exposure to endocrine-active compounds, including aberrant gonadal morphology (e.g., the presence of oocytes in the testis, alterations in Leydig and Sertoli cell morphology or number) (54, 55). This literature documents the endocrine-disruptive effects of a wide array of commercial chemicals and by-products, including pesticides; sewage contaminants, such as surfactants (e.g., octylphenol and nonylphenol) and pharmaceutical agents; plasticizers (e.g., phthalates); flame retardants (e.g., PCBs, polybrominated diphenol ethers, tetrabromobisphenol A), and industrial pollutants (e.g., heavy metals, dioxin, polycyclic aromatic hydrocarbons) [for reviews, see (3, 6, 56–58)]. Furthermore, these effects were caused by exposure to levels of chemicals found in the environment.

CONCERNING TRENDS

There have been a number of concerning trends in human reproductive health. The incidence of testis cancer, primarily a disease of young men, has increased in Europe, with a lifetime risk approaching 1% (59). In addition, young men born today in Europe have remarkably low average sperm counts and a high prevalence (approximately one in six) of abnormally low sperm counts likely to cause fertility problems (60). New data in three cities (Boston, MA, US, Copenhagen, Denmark, and Turku, Finland) demonstrate a significant secular trend in serum testosterone (61–63). The details vary somewhat, but together these studies suggest that testosterone has declined about 1% per year for the past 40–50 years. This decline is consistent with the reduction in sperm concentration reported by Carlsen in 1992 (64), and these two trends, taken together, increase the plausibility of a significant decrease in male reproductive function. For girls in the US, there has been a reported decline in age of onset of breast development and menarche over the last 30 years (65). Rapid changes in health endpoints are of concern because they suggest environmental and lifestyle, and thus avoidable, causes.

COMPELLING NEW SCIENCE: MOVING BEYOND GENETIC DETERMINANTS

Genetic mutations are known to alter gene expression and lead to disease. Environmental exposures have typically been thought of as influencing genetics and health by causing mutations. For example, it has long been known that radiation leads to genetic mutations and increased risk of disease, such as cancer.

However, research during the past decade has revealed that many environmental exposures also act through modification of the epigenome (the collection of biochemical reactions that determine the gene expression) of cells, leading to either immediate or latent adverse effects on reproduction. For example, recent epigenetic research has revealed a possible mechanism by which in utero exposure to BPA heightens susceptibility to prostate cancer in adult rats: BPA alters the normal process of silencing, through hypermethylation, the phosphodiesterase type 4 variant 4 gene that occurs with aging, thus elevating gene expression (66). BPA also permanently alters expression of HOXA10, a gene necessary for uterine development (67). Epigenetic studies have also shown that DES causes alterations in uterine tissue

architecture and morphology and heightens susceptibility to uterine adenocarcinoma by inducing permanent changes in several estrogen-responsive genes (28). These are but a few examples of how the field of epigenetics has and will continue to contribute to our mechanistic understanding of the impact of environmental contaminants on reproductive health.

ENVIRONMENTAL CONTAMINANTS AND EFFECTS IN MALES

Reproductive Effects of Early Life Exposures

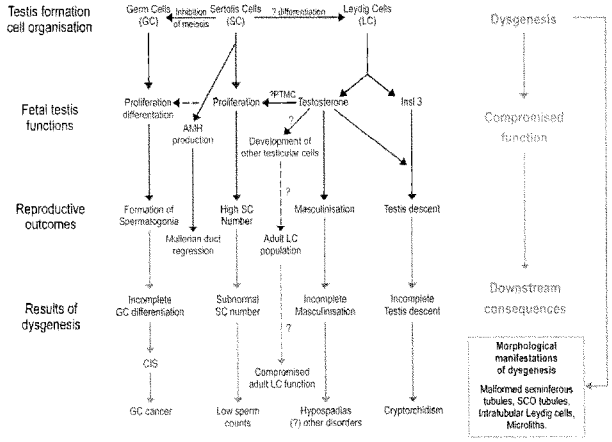
Testicular development and the environment Over the past 10–15 years, the central role that deficient androgen production or action during fetal testis development may play in the origin of reproductive disorders has been well documented, and is reviewed in Sharpe and Skakkebaek (68).

There is a relatively high incidence of male reproductive disorders that manifest at birth (cryptorchidism, hypospadias) or in young adulthood [testicular germ cell cancer (TGCC) and infertility] (69, 70). These four disorders are increasing in prevalence in the West (69). They are risk factors for each other and they share several, pregnancy-related risk factors (68–70). Skakkebaek et al. hypothesize that TGCC, cryptorchidism, and some cases of hypospadias and low sperm count comprise a testicular dysgenesis syndrome (TDS) with a common origin in fetal life (69). The hypothesis proposes that "abnormal testis development (dysgenesis), which could have numerous primary causes, leads secondarily to hormonal or other malfunctions of the Leydig and Sertoli cells during male sexual differentiation, leading to increased risk of reproductive disorders of the testicular system" (Fig. 3) (68–70).

This hypothesis has been supported by findings in an animal model of TDS involving fetal exposure to the phthalate DBP as well as by new clinical studies described in Sharpe and Skakkebaek (68). Exposure of rats in utero to DBP induces a TDS-like syndrome in the male offspring (71–73); this is manifest as dose-dependent induction of cryptorchidism, hypospadias, and impaired spermatogenesis and infertility. Focal dysgenesis (73, 74), subnormal fetal Leydig cell function (71–73), and subnormal Sertoli cell proliferation (75) and possibly function (73), consistent with changes predicted in the TDS hypothesis, are also demonstrated (69).

FIGURE 3

Schematic diagram to illustrate how dysgenesis of the early fetal testis is thought to lead to abnormalities of somatic cell function, resulting in hormonal changes and the downstream disorders that comprise testicular dysgenesis syndrome (TDS). The central role of testosterone is highlighted by the blue boxes. Dashed lines show pathways that are hypothesized but unproven (Adapted from Sharpe and Skakkebaek [68]).



Abbreviations: PTMC = peritubular myoid cell; Insl3 = insulin-like factor 3; AMH = anti-müllerian hormone; CIS = carcinoma-in-situ; SCO = Sertoli cell only.

Woodruff. Environmental reproductive health. Fertil Steril 2008.

Furthermore, the characteristics of the focal dysgenesis induced by fetal DBP exposure in rats (73, 74)—malformed seminiferous cords, Sertoli cell-only tubules with immature-appearing Sertoli cells and the abnormal occurrence of intratubular Leydig cells—are all also reported in the testes of men with TGCC (76–78).

A particularly important recent development is the observation that inhibition of androgen production or action in rodents, resulting from transgenesis (79), DBP exposure (75), or flutamide treatment (80), reduces Sertoli cell numbers substantially in the perinatal period and leads to downstream TDS disorders. Thus, androgens appear to play a determining role during the most important periods of Sertoli cell proliferation (fetal and early postnatal life) (68, 81) (Fig. 3). This finding is consistent with data in humans showing that Sertoli cell number increases during fetal life (when testosterone levels are high) and during the period of the neonatal testosterone rise (81, 82). Because Sertoli cell number in adulthood is the primary determinant of sperm production and counts in men (81), it is hypothesized that reduction in testosterone levels in the fetal testis, as a secondary consequence of dysgenesis, could lead to reduced Sertoli cell numbers and, consequently, low sperm counts in adulthood (Fig. 3). This is an important finding, because Sertoli cells in the fetal testis in all species so far examined do not express androgen receptors. Therefore, antiandrogens appear to exert toxic effects on male reproductive development through multiple pathways (75).

The TDS syndrome is further supported by studies that induce hypospadias in CD1 mice through exposure to EDCs during the critical period of urethral development. These chemicals include 17α estradiol; pesticides, such as vinclozolin; pharmaceutical products, such as the antihistamine loratadine; and the flame retardant benzophenone-2 (83). A recent human study by Swan et al. (84) found in utero exposure to phthalates associated with shortened (and thus less masculine) male anogenital distance, which has also been observed in numerous animal studies.

Based on the increasing prevalence of TDS disorders and recent evidence for declining testosterone levels in men, endocrine disrupting chemicals in our environment are likely to become ever more important in shaping the reproductive health of young men in the present and next generation.

Prostate development and the environment Similar to the testis, male accessory sex glands and organs are also vulnerable to environmental EDCs, with adverse effects manifesting in adulthood. The developing prostate gland is particularly sensitive to estrogens, and high-dose exposure during a critical developmental window results in prostatic intraepithelial neoplasia in adult rodent models (85). Early-life exposure to estrogenic substances could sensitize the developing prostate to later risks from increased estrogen levels that occur in the aging male. A study of rats treated neonatally to BPA followed by hormones that mimic the aging male in adulthood showed a significantly higher prostatic intraepithelial neoplasia incidence and score compared with controls (rats exposed only to BPA neonatally or those given only the aging hormones in adulthood) (86). As discussed above, this heightened predisposition to prostate carcinogenesis results from permanent alterations to the prostate epigenome (66).

Reproductive Effects of Adult Exposures

Hauser and Sokol (87) review human and animal evidence on exposure to several classes of environmental contaminants during adulthood and adverse male reproductive outcomes. In the past two decades, numerous animal and clinical studies have provided evidence that a variety of chemicals can disrupt the hypothalamic–pituitary–testicular axis by acting as hormonal antagonists or agonists or by disrupting the biochemical processes regulating hormone secretion (87).

Consistent with the effects of prenatal exposure discussed above, rodent models of pubertal and adult exposure to phthalates report testicular toxicity characterized by testicular atrophy, reduced sperm counts, altered Leydig cell structure and function, Sertoli cell toxicity, and increased germ cell apoptosis (68). These studies indicate an age-dependent sensitivity to exposure, with prenatal exposure causing the most, and adult exposures the least, severe effects. Studies of phthalate exposure and male reproductive health in humans are limited and inconsistent. For example, certain phthalate metabolites (MBP and MBzP) were associated with decreased sperm quality among US (88) but not among Swedish men (89). The differences across studies, such as the ages of the population (older in the US) or the source of the men (general population in Sweden and infertile couples in the US), may account for some of the differences in study results, but may also suggest that a subpopulation of men may have increased susceptibility to phthalate exposure (87).

PCBs are another industrial contaminant for which data on prenatal and adult exposures in humans are available. For example, epidemiologic studies of high-dose exposures from accidental food contamination report abnormal sperm morphology, higher oligozoospermia rates, and reduced hamster oocyte penetration 20 years after exposure (90). Effects on sperm quality resulting from prenatal exposure were similar: abnormal morphology, decreased motility, and reduced hamster oocyte penetration (91). Studies to date of lower dose, environmental exposures to PCBs support an association with reduced semen quality, specifically reduced sperm motility (92).

Heavy metals such as lead were among the first recognized human reproductive toxicants (93). Animal, clinical, and epidemiologic studies have demonstrated that exposure to lead disrupts all levels of the reproductive axis, with the central nervous system and testis appearing to be the most sensitive organs and puberty a critical window of susceptibility (94–96). Epidemiologic studies report a dose-related suppression of spermatogenesis, normal or decreased serum testosterone, and inappropriately normal urinary gonadotropins in the face of low testosterone levels in men with higher blood lead

levels (97). Recent findings suggest that lead may also induce chromosomal abnormalities and cause infertility by interfering with the acrosome reaction in spermatozoa (98). Human studies evaluating other heavy metals suggest that cadmium, mercury, and boron may also disrupt male reproduction (99).

Dibromochloropropane (DBCP) is the most characterized agricultural chemical with respect to male reproductive toxicity. Occupational exposure to DBCP produced: azoospermia and oligospermia, germinal epithelium damage, genetic alterations in sperm (such as double Y-bodies), male subfertility, increased rates of spontaneous abortions in wives of exposed workers, hormonal imbalances, and altered sex ratio in offspring (100). Reversibility of effects following cessation of exposure are variable (101, 102). The reproductive toxicity of other agricultural chemicals such as organophosphate pesticides, vinclozolin, and DDT is less well characterized in humans; nevertheless, animal and human studies demonstrate these chemicals to have adverse effects on semen quality as well as antiandrogen properties (100).

Additional classes of chemicals that are of particular interest because of widespread human exposure and animal evidence of reproductive toxicity, but for which human data are lacking or minimal, include: those used in consumer products, such as BPA, parabens, and phthalates; pyrethroid pesticides; and air pollution (87).

ENVIRONMENTAL CONTAMINANTS AND EFFECTS IN FEMALES

Reproductive Effects of Early-Life Exposures

Prenatal exposure to environmental factors can modify normal cellular and tissue development and function through developmental programming, such that women may have a higher risk of reproductive pathologies and metabolic and hormonal disorders later in life (23–27). Woodruff and Walker (28) review new research on the effects of environmental estrogen exposure, during key developmental windows of susceptibility, on normal reproductive development of the ovaries and the uterus, and on the link to specific disease states in the adult.

Ovarian follicular development and the environment The ovarian follicle is the functional unit of the ovary, and is comprised of an oocyte surrounded and supported by the somatic granulosa and theca cells (28). The health of the follicle can impact the health of the woman as well as the health of her offspring. For example, decreased numbers of follicles, multioocyte follicles, and incomplete follicular development can all result in decreased fertility. The precise mechanisms involved in early ovarian follicle formation are not known, but are essential in organizing the fetal ovary and establishing the postnatal follicle number that will provide the female with sufficient oocytes for a lifetime of fertility (28).

Estrogen and activin are two known factors that play an important role in regulating oocyte and follicle development and function (103–112), and aberrant development and ovarian pathologies are observed in mice exposed to neonatal estrogen or activin. Neonatal exposure of rats to estradiol benzoate has been show to delay follicle and interstitial development (113). Neonatal exposure to DES or the natural estrogen estradiol results in lack of corpora lutea in adult mice (114), suggesting that these effects persist beyond reproductive tract development and impact fertility in the adult. Neonatal exposure to DES, estradiol, or the phytoestrogen genistein also induces formation of multioocytic follicles in mice (115–117)—an effect that is also reported in alligators exposed to environmental estrogenic contaminants (see above) (46). Additionally, activin administered during the critical, postnatal period of primordial follicle formation changes the number of postnatal follicles (28, 118). Current mechanistic studies are exploring whether neonatal estrogen exposure alters activin signaling in the ovary; preliminary findings of decreased activin subunit gene expression and impacted activin signaling in the mouse ovary support this hypothesis (28).

Uterus development and the environment Women exposed to DES in utero during critical periods of reproductive tract development developed several types of reproductive tract abnormalities, as well as an increased incidence of cervical–vaginal cancer later in life (118). Animal studies that simulate the human DES experience have since shown that exposure of the developing reproductive tract of CD1 mice to DES imparts a permanent estrogen imprint that alters reproductive tract morphology, induces persistent expression of the lactoferrin and c-fos genes, and induces a high incidence of uterine adenocarcinoma (119–121). Experiments in rats have shown exposure to DES during the critical window of uterine development leaves a hormonal imprint on the developing uterine myometrium in rats that were genetically predisposed to uterine leiomyoma (28), increasing the risk for adult uterine leiomyoma from 65% to >90% and increasing tumor multiplicity and size (35). DES-induced developmental programming appears to require the estrogen receptor α (122), suggesting that signaling through this receptor is crucial for establishing developmental programming.

Studies have now been extended beyond DES to demonstrate that other environmental estrogens reprogram gene expression in the uterus (28): exposure to genistein and BPA during the window of maximum sensitivity to developmental programming induces the expression of the estrogen-responsive genes calbindin and progesterone receptor. Neonatal BPA exposure attenuated estrogen-responsive genes, whereas genistein exposure induced an even higher level of estrogen responsiveness than DES exposure. In contrast to DES, exposure to these environmental estrogens does not disrupt ovarian function in adult females, which continue to cycle normally.

Reproductive Effects of Adult Exposures

Mendola et al. (123) review the growing body of epidemiologic and occupational studies showing that environmental exposures can interfere with all developmental stages of

reproductive function in adult females, including puberty, menstruation and ovulation, fertility and fecundity, and menopause.

Puberty Environmental contaminants can accelerate or delay pubertal development. Lead exposure delays puberty in girls, even at very low levels (<5 micrograms per deciliter) (124–126). Earlier age at puberty has been associated with exposure to with phthalates (127), DDT (128), DDE (129), and PCBs (126).

Menstrual and ovarian function Variations in menstrual and ovarian function have been observed following consumption of drinking water disinfection byproducts and fish contaminated with PCBs and other pollutants; similar associations were noted in studies using biologic markers of 2,3,7,8 tetrachlorodibenzo-*p*-dioxin (TCDD), DDT, DDE, and PCBs (123). These studies generally describe functional variations (e.g., long or short cycles, changes in luteal or follicular phase) that indicate an underlying perturbation of hormones rather than the development of clinical disorders, although long-term effects are not known.

Shorter cycles have been observed for occupational exposure to lead (130) and to chlordibromoethane in drinking water (131). Longer cycles have been observed in studies of EDCs such as TCDD (132), hormonally active pesticides (133), serum PCBs (134), and multiple industrial chemicals (e.g., ethylene glycol ethers) used in the semiconductor industry (135). Menstrual disorders such as missed periods and abnormal uterine bleeding were also observed (130, 133, 134). Other studies found menstrual abnormalities, such as abnormal menstrual bleeding with no change in cycle length, associated with PCBs or metal exposure (136, 137).

Follicle-stimulating hormone is decreased in women exposed to pentachlorophenol (138). Progesterone and estrogen are reduced in women exposed to DDT and DDE (139, 140).

Endometriosis has been widely studied in relation to environmental exposures, beginning with dioxin-induced endometriosis in monkeys. Most studies considering PCBs have found increased serum levels among endometriosis cases, compared with controls (123). Phthalate esters have also been associated with endometriosis among some women (141, 142).

Fertility and fecundity Fertility and fecundity studies include time to pregnancy and spontaneous abortion outcomes as well as studies of infecundity and other measures of subfertility (123). Lead is consistently observed to be a reproductive toxicant, causing decreased fertility and increased pregnancy loss (130, 143). Pregnancy loss has also been associated with DDE in most studies (144–146).

Working with or applying pesticides, primarily in agricultural and horticultural settings, appears to consistently reduce fertility and fecundability (147–152). Preconception exposure, but not exposure during pregnancy (153), appears to elevate risk for spontaneous abortion (154). Pesticides are detrimental to both fecundity and fertility in the limited number of animal studies conducted to date (155, 156).

Additional environmental exposures, including solvents, radiation, and other compounds, are also associated with decrements in human female fertility, but the literature is limited or inconclusive (123). In particular, studies on solvent exposure in a variety of settings (157–159) suggest decreases in fertility. One study found an increase in recurrent miscarriage associated with BPA (160), a finding that is consistent with the disruption of oogenesis through meiotic disruption and aneuploidy in mice exposed to environmentally relevant levels of BPA (161, 162).

Menopause Menopause has not been extensively studied, but earlier age at menopause has been observed with exposure to serum dioxin (163), DDT, DDE, and other pesticides (164–166). Animal studies report disruption of folliculogenesis in mice exposed to lead (167) as well as follicle destruction after exposures to mancozeb, dibromoacetic acid, polycyclic aromatic hydrocarbons, cyclophosphamide, and 4-vinylcyclohexene diepoxide (168–173), suggesting possible mechanisms relevant to human disorders associated with these exposures.

ENVIRONMENTAL EXPOSURES DURING PREGNANCY AND ADVERSE BIRTH OUTCOMES

Windham and Fenster (174) review the epidemiologic literature on exposure to certain environmental contaminants during pregnancy and adverse birth outcomes, such as low birth weight, intrauterine growth retardation (IUGR), preterm delivery, and stillbirth.

Exposure to Environmental Tobacco Smoke (ETS) reduces mean birth weight (slightly increasing the risk of IUGR), and increases the risk of preterm delivery (175, 176). Studies of water disinfection byproducts support an association between exposure and IUGR, with little consistent effect on preterm delivery (174, 177–179). The weight of epidemiologic evidence also suggests that high levels of exposure to DDT or DDE is associated with adverse fetal growth outcomes and preterm delivery (174). Studies of organophosphate exposure and reproductive outcomes have suffered from lack of a standard validated measure of exposure. However, despite inconsistencies in study results, the weight of evidence and precautionary principle suggest that exposure to organophosphates should be avoided during pregnancy (174).

MOVING FORWARD

At the *Summit*, participants from research, academic, health care, government, advocacy, and community sectors identified the most important needs and directions for advancing reproductive environmental health through research, health care, policy, community action, and occupational health.

Research

Participants in the research break-out group focused on identifying the critical research directions and key needs for advancing the science database on environmental reproductive health. They identified priority actions in two main areas: communication and research priorities that will benefit from continued dialogue among government agencies, basic scientists, epidemiologists, clinicians, and the general public, who all have critical voices in the discussion.

1. There is a need for better communication to foster collaborations:

To enhance collaborations among researchers and between researchers and granting agencies, the group proposed the following.

- Foster technologies that encourage collaboration, such as listservs and Web-based databases of tissue banks.
- Work with government agencies and universities to promote collaboration among researchers, such as broadening the definition of a principal investigator to include project leaders in a program project or center grant.
- Develop opportunities for researchers to meet and discuss collaborations in environmental reproductive health research, such as at professional society meetings.

2. Critical research directions in environmental reproductive health

The following priorities were identified:

- Human and animal studies that are longitudinal and take into account the full life cycle, including prenatal exposures (e.g., The National Children's Health Study).
- Leverage existing mechanisms of data collection to incorporate semen analysis into the US Centers for Disease Control and Prevention's NHANES study.
- Biologic measurement collection and banking should be incorporated into epidemiologic study designs for future research.
- Development of biomarkers of exposure and preclinical indicators of disease in animals and humans, and better biomarkers of human fertility.
- Strategies to address regulatory obstacles such as interpreting and working with the Health Insurance Portability and Accountability Act rules.
- Increased funding for emerging areas of research on individual and mixtures of chemicals and their effects on the epigenome; fetal programming and transgenerational effects; low-dose effects; nontraditional dose–response curves; and crosstalk among endocrine systems and receptors.
- Develop systems to identify new emerging contaminants.

Health Care Professionals

Participants in this break-out group, comprised primarily of health professionals and health-affected groups or patient advocates, discussed what health care professionals need in order to educate and advocate for patients. Participants agreed that:

- Health care professionals need to be well-informed about the sources and effects of environmental and workplace contaminant exposures, especially in relation to periconceptional, prenatal, early infancy, and childhood windows of susceptibility.
- Because of the complexity of analyzing exposures and difficulty in predicting precise health effects in a given individual, health care professionals must address uncertainty when communicating with patients on these issues.
- Health care professionals need to take a precautionary stance and provide patients specific advice on avoiding exposures.
- Health care professionals and scientists can help interpret complex scientific research for legislators and the public to support better regulation of contaminants, leading to reduced exposures.

Some important needs of health care professionals include:

- Clear, simple-to-use health information tools that list contaminants and sources of exposure, ways to reduce exposures, and health effects of specific exposures. Tools need to be developed collaboratively by scientists, health care professionals, and advocacy and community groups to be relevant and appropriate to a diversity of populations.
- Education on reproductive environmental health should be included in medical, nursing, and public education.
- Health care professionals should take a work history and inquire about patients' exposures, ideally *before* pregnancy. This is not the current standard of practice.

Examples of health information tools available to health professionals The Pediatric Environmental Health Tool Kit provides easy to use, anticipatory, age-appropriate guidance on how to minimize harmful pediatric environmental exposures (http://psr.igc.org/ped-env-hlth-toolkit-project.htm). The Hazard Evaluation System and Information Service is comprised of informational materials, training, and a workplace hazard helpline for workers and health professionals for a number of workplace reproductive and developmental hazards (http://www.dhs.ca.gov/ohh/HESIS/hesispubs.htm.).

Policy

Participants from all sectors represented at the *Summit* identified four key policy needs:

1) Advance models for comprehensive chemicals evaluation at local, state, and national levels and develop effective chemical regulation.

Because there is such a lack of data on chemicals that are already on the market, comprehensive testing should be required for chemicals remaining on the market, and premarket testing should include reproductive environmental health outcomes. The testing should evaluate effects on both the

environment and human health, assess exposures at different stages of development, and identify cumulative and synergistic impacts. The review of the testing results needs to include mechanisms for reducing, limiting, or removing chemicals that pose reproductive health risks.

2) Improve the science base: increase resources and improve methods to enhance research on environmental reproductive health.

Key areas include developing improved and faster screening technologies to more quickly identify potentially harmful chemicals and improving research design to: better identify developmental effects that can occur from exposures during important reproductive windows; track impacts that can be passed on through multiple generations; and assess low-dose effects and effects from multiple exposures to chemicals.

3) Improve the use of science in decision making.

Participants noted that there are a number of steps between development of scientific findings and then using those findings to make policy decisions. The process for doing this can be complicated and highly technical. Further efforts should focus on acknowledging uncertainty in the science and allowing for action in the face of this uncertainty, increasing steps to limit undue influence or bias in the review and synthesis process, and incorporating low-dose effects and exposure to multiple chemicals into decision making and risk assessment.

4) Right to know: improve information given to consumers and workers on environmental contaminants in products.

Participants identified the need to address the inadequacies of consumer product labeling and Material Safety Data Sheets, as well as the obstacles that trade secret protections place on accessing information on consumer product ingredients.

Community Action

Summit participants gathered to talk about the science in the context of environmental justice, occupational health, and reproductive justice. Participants noted that learning about potentially hazardous chemicals in everyday products and in the workplace and their effects on babies in utero are powerful personal motivators toward further education and activism. However, placing the responsibility on individuals to avoid everyday toxins such as mercury in fish or hazardous chemicals in common household products is not an effective strategy for protecting reproductive health. Efforts by community members, scientists, epidemiologists, clinicians, activists, communications strategists, and spokespeople will be more successful if they work toward a reformed and improved public health policy that adequately regulates chemicals and reduces exposures.

Safe Work

Participants in the Safe Work break-out group discussed the implications of the science and key needs for improving worker health and safety. The group noted that more attention needs to be paid to workers' exposure within the area of environmental health. Their discussion also echoed themes from some of the other groups, such as the need for better communication of the science and improved methods for making decisions in the face of uncertainty that consider worker health. They also identified some unique needs of workers and proposed the following:

- Reduce permissible exposure levels to chemicals that harm reproduction and development so that they are more in line with environmental exposure limits. In addition, permissible exposure limits should reflect the toxicity of exposure to mixtures of chemicals used in the workplace, rather than exposure to chemicals individually.
- Exposure assessment and monitoring in occupational settings should be expanded.
- Expand occupational health researchers' access to workers so that health consequences can be identified and corrected.
- Develop alliances that can improve health across different sectors. For example, making the connection between worker safety and hospital patient safety (concerning phthalates) and fostering alliances between environmental health groups and labor and worker groups.

CONCLUSION

In conclusion, the UCSF-CHE *Summit on Environmental Challenges to Reproductive Health and Fertility* provided a view of critical scientific information that underscores the need for further efforts to improve reproductive health. One common theme throughout the *Summit* was communication and collaboration. Scientists bring unique and important contributions to studying the impact of environmental contaminants on reproductive health. A goal of moving forward from the *Summit* is to bring together epidemiologists, basic scientists, clinicians, and clinical researchers to approach the study of environmental contaminants on reproductive health in an integrated way. However, such research is most valuable, and could be of highest benefit for human health, if it is conducted in collaboration with health-affected and community-based groups that can facilitate focusing research questions on the most pressing issues of the most affected constituencies. Communication across scientific disciplines and to among scientists, health care providers, health-affected groups, and the public, as well as efforts in research, education, and policy, are key to reducing the adverse impacts of environmental contaminants and to enhancing the reproductive health of this and future generations.

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REFERENCES

1. Proceedings of the UCSF-CHE Summit on Environmental Challenges to Reproductive Health and Fertility. Fertil Steril 2008;89(Suppl 1). Available online at http://www.fertstert.org.
2. US EPA. What is the TSCA Chemical Substanee Inventory. Vol. 2007. Washington, DC: US Environmental Protection Agency, 2006.
3. McLachlan JA. Environmental signaling: what embryos and evolution teach us about endocrine disrupting chemicals. Endocr Rev 2001;22: 319–41.
4. Zoeller RT, Dowling ALS, Herzig CTA, Iannacone EA, Gauger KJ, Bansal R. Thyroid hormone, brain development, and the environment. Environ Health Perspect 2002;110(Suppl 3):355–61.
5. Gray LE Jr, Wilson VS, Stoker T, Lambright C, Furr J, Noriega N, et al. Adverse effects of environmental antiandrogens and androgens on reproductive development in mammals. Int J Androl 29:96–104.
6. Guillette LJ Jr, Gunderson MP. Alterations in the development of the reproductive and endocrine systems of wildlife exposed to endocrine disrupting contaminants. Reproduction 2001;122:857–64.
7. Fournier M, Brousseau P, Tryphonas H, Cyr D. Biomarkers of immunotoxicity: an evolutionary perspective. In: Guillette LJ Jr, Crain DA, eds. Endocrine disrupting contaminants: an evolutionary perspective. Philadelphia, PA: Francis and Taylor Inc., 2000:182–215.
8. Guillette LJ Jr. Endocrine disrupting contaminants—beyond the dogma. Environ Health Perspect 2006;114(Suppl 1):9–12.
9. Osteen KG, Sierra-Rivera E. Does disruption of immune and endocrine systems by environmental toxins contribute to development of endometriosis? Semin Reprod Endocrinol 1997;15:301–8.
10. Edwards TM, Myers JP. Environmental exposures and gene regulation in disease etiology. Environ Health Perspect 2007;115:1264–70.
11. Anway MD, Cupp AS, Uzumcu M, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science 2005;308:1466–9.
12. Crews D, Gore AC, Hsu TS, Dangleben NL, Spinetta M, Schallert T, et al. Transgenerational epigenetic imprints on mate preference. Proc Nat Acad Sci USA 2007;104:5942–6.
13. CDC. Third national report on human exposure to environmental chemicals. Atlanta, GA: Centers for Disease Control and Prevention, 2005.
14. Howdeshell KL, Furr J, Lambright CR, Rider CV, Wilson VS, Gray LE Jr. Cumulative effects of dibutyl phthalate and diethylhexyl phthalate on male rat reproductive tract development: altered fetal steroid hormones and genes. Toxicol Sci 2007;99:190–202.
15. Morford LL, Henck JW, Breslin WJ, DeSesso JM. Hazard identification and predictability of children's health risk from animal data. Environ Health Perspect 2004;112:266–71.
16. Louis RH. Periconception window: advising the pregnancy planning couple. Fertil Steril. In press.
17. Calabrese EJ. Sex differences in susceptibility to toxic industrial chemicals. Br J Ind Med 1986;43:577–9.
18. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. Int J Epidemiol 2002;31:285–93.
19. Cook JD, Davis BJ, Goewey JA, Berry TD, Walker CL. Identification of a sensitive period for developmental programming that increases risk for uterine leiomyoma in Eker rats. Reprod Sci 2007;14:121–36.
20. Barker DJ. Fetal origins of coronary heart disease. BMJ 1995;311: 171–4.
21. Robinson R. The fetal origins of adult disease. BMJ 2001;322:375–6.
22. Hanson M, Gluckman P, Bier D, Challis J, Fleming T, Forrester T, et al. Report on the 2nd world congress on fetal origins of adult disease, Brighton, UK, June 7–10, 2003. Pediatr Res 2004;55:894–7.
23. Gluckman PD, Hanson MA. Living with the past: evolution, development, and patterns of disease. Science 2004;305:1733–6.
24. Couzin J. Quirks of fetal environment felt decades later. Science 2002;296:2167–9.
25. Barker DJ. Fetal programming of coronary heart disease. Trends Endocrinol Metab 2002;13:364–8.
26. Frankel S, Elwood P, Sweetnam P, Yarnell J, Smith GD. Birthweight, body-mass index in middle age, and incident coronary heart disease. Lancet 1996;348:1478–80.
27. Hattersley AT, Tooke JE. The fetal insulin hypothesis: an alternative explanation of the association of low birthweight with diabetes and vascular disease. Lancet 1999;353:1789–92.
28. Woodruff TK, Walker CL. Fetal and early postnatal environmental exposures and reproductive health effects in the female. Fertil Steril. In press.
29. Miller C, Degenhardt K, Sassoon DA. Fetal exposure to DES results in de-regulation of Wnt7a during uterine morphogenesis. Nat Genet 1998;20:228–30.
30. Pavlova A, Boutin E, Cunha G, Sassoon D. Msx1 (Hox-7.1) in the adult mouse uterus: cellular interactions underlying regulation of expression. Development 1994;120:335–45.
31. Taylor HS, Vanden Heuvel GB, Igarashi P. A conserved Hox axis in the mouse and human female reproductive system: late establishment and persistent adult expression of the Hoxa cluster genes. Biol Reprod 1997;57:1338–45.
32. Schrager S, Potter BE. Diethylstilbestrol exposure. Am Fam Physician 2004;69:2395–400.
33. Newbold RR, Tyrey S, Haney AF, McLachlan JA. Developmentally arrested oviduct: a structural and functional defect in mice following prenatal exposure to diethylstilbestrol. Teratology 1983;27:417–26.
34. Baird DD, Newbold R. Prenatal diethylstilbestrol (DES) exposure is associated with uterine leiomyoma development. Reprod Toxicol 2005;20:81–4.
35. Cook JD, Davis BJ, Cai SI, Barrett JC, Conti CJ, Walker CL. Interaction between genetic susceptibility and early-life environmental exposure determines tumor-suppressor-gene penetrance. Proc Natl Acad Sci USA 2005;102:8644–9.
36. McLachlan JA, Newbold RR, Bullock BC. Long-term effects on the female mouse genital tract associated with prenatal exposure to diethylstilbestrol. Cancer Res 1980;40:3988–99.
37. Newbold RR, Hanson RB, Jefferson WN, Bullock BC, Haseman J, McLachlan JA. Increased tumors but uncompromised fertility in the female descendants of mice exposed developmentally to diethylstilbestrol. Carcinogenesis 1998;19:1655–63.
38. Newbold RR, Hanson RB, Jefferson WN, Bullock BC, Haseman J, McLachlan JA. Proliferative lesions and reproductive tract tumors in male descendants of mice exposed developmentally to diethylstilbestrol. Carcinogenesis 2000;21:1355–63.
39. Titus-Ernstoff L, Troisi R, Hatch EE, Wise LA, Palmer J, Hyer M, et al. Menstrual and reproductive characteristics of women whose mothers were exposed in utero to diethylstilbestrol (DES). Int J Epidemiol 2006;35:862–8.
40. Blatt J, Van Le L, Weiner T, Sailer S. Ovarian carcinoma in an adolescent with transgenerational exposure to diethylstilbestrol. J Pediatr Hematol Oncol 2003;25:635–6.
41. Brouwers MM, Feitz WF, Roelofs LA, Kiemeney LA, de Gier RP, Roeleveld N. Hypospadias: a transgenerational effect of diethylstilbestrol? Hum Reprod 2006;21:666–9.
42. Klip H, Verloop J, van Gool JD, Koster ME, Burger CW, van Leeuwen FE. Hypospadias in sons of women exposed to diethylstilbestrol in utero: a cohort study. Lancet 2002;359:1102–7.
43. Colborn T, Dumanoski D, Myers JP. Our stolen future. New York: Penguin Books, 1996.

44. Guillette LJ Jr, Edwards TM. Environmental influences on fertility: can we learn lessons from studies of wildlife? Fertil Steril. In press.
45. Colborn T, vom Saal FS, Soto AM. Developmental effects of endocrine-disrupting chemicals in wildlife and humans. Environ Health Perspect 1993;101:378–84.
46. Guillette LJ Jr, Gross TS, Masson GR, Matter JM, Percival HF, Woodward AR. Developmental abnormalities of the gonad and abnormal sex hormone concentrations in juvenile alligators from contaminated and control lakes in Florida. Environ Health Perspect 1994;102:680–8.
47. Guillette LJJ, Moore BC. Contaminants, fertility and multioocytic follicles: a lesson from wildlife? Semin Reprod Med 2006;24:134–41.
48. Iguchi T. Cellular effects of early exposure to sex hormones and anti-hormones. Int Rev Cytol 1992;139:1–57.
49. Matter JM, Crain DA, Sills-McMurry C, Pickford DB, Rainwater TR, Reynolds KD, et al. Effects of endocrine-disrupting contaminants in reptiles: alligators. In: Kendall R, Dickerson R, Giesy J, Suk W, eds. Principles and processes for evaluating endocrine disruption in wildlife. Pensacola, FL: SETAC Pr., 1998:267–89.
50. Milnes MR, Bryan TA, Medina JG, Gunderson MP, Guillette LJ Jr. Developmental alterations as a result of in ovo exposure to the pesticide metabolite p,p′-DDE in *Alligator mississippiensis*. Gen Comp Endocrinol 2005;144:257–63.
51. Stoker C, Rey F, Rodrigoez H, Ramos JG, Sirosky P, Larriera A, et al. Sex reversal effects on *Caiman latirostris* exposed to environmentally relevant doses of the xenoestrogen bisphenol A. Gen Comp Endocrinol 2003;133:287–96.
52. Willingham E, Crews D. Sex reversal effects of environmentally relevant xenobiotic concentrations on the red-eared slider turtle, a species with temperature-dependent sex determination. Gen Comp Endocrinol 1999;113:429–35.
53. Willingham E, Rhen T, Sakata JT, Crew D. Embryonic treatment with xenobiotics disrupts steroid hormone profiles in hatchling red-eared slider turtles (*Trachemys scripta elegans*). Environ Health Perspect 2000;108:329–32.
54. Jobling S, Beresford N, Nolan M, Rodgers-Gray TP, Brighty G, Sumpter J, et al. Altered sexual maturation and gamete production in wild roach (*Rutilus rutilus*) living in rivers that receive treated sewage effluents. Biol Reprod 2002;66:272–81.
55. Mylchreest E, Sar M, Wallace DG, Foster PMD. Fetal testosterone insufficiency and abnormal proliferation of Leydig cells and gonocytes in rats exposed to di(n-butyl) phthalate. Reprod Toxicol 2002;16:19–28.
56. Tyler CR, Jobling S, Sumpter JP. Endocrine disruption in wildlife: A critical review of the evidence. Crit Rev Toxicol 1998;28:319–61.
57. Iguchi T, Watanabe H, Katsu Y. Developmental effects of estrogenic agents on mice, fish and frogs: a mini-review. Horm Behav 2001;40:248–51.
58. Milnes MR, Bermudez DS, Bryan TA, Edwards TM, Gunderson MP, Larkin IV, et al. Contaminant-induced feminization and demasculinization of nonmammalian vertebrate males in aquatic environments. Environ Res 2006;100:3–17.
59. Bray F, Richiardi L, Ekbom A, Pukkala E, Cuninkova M, Moller H. Trends in testicular cancer incidence and mortality in 22 European countries: continuing increases in incidence and declines in mortality. Int J Cancer 2006;118:3099–111.
60. Jorgensen N, Asklund C, Carlsen E, Skakkebaek NE. Coordinated European investigations of semen quality: results from studies of Scandinavian young men is a matter of concern. Int J Androl 2006;29:54–61; discussion 105–8.
61. Andersson A, Jensen TK, Petersen JH, Joergensen T, Borch-Johnsen K, Skakkebaek NE. Trends in Leydig cell function in Danish men. Hum Reprod 2005;20:i26–7.
62. Perheentupa A, Laatikainen T, Vierula M, Skakkebaek NE, Andersson AM, Toppari T. Clear birth cohort effect in serum testosterone and SHBG levels in Finnish men. Endocrine Society Meeting 2006, 2006.
63. Travison TG, Araujo AB, O'Donnell AB, Kupelian V, McKinlay JB. A population-level decline in serum testosterone levels in American men. J Clin Endocrinol Metab 2007;92:196–202.
64. Carlsen E, Giwercman A, Keiding N, Skakkebaek NE. Evidence for decreasing quality of semen during past 50 years. BMJ 1992;305:609–13.
65. Herman-Giddens ME. Recent data on pubertal milestones in Unite States children: the secular trend toward earlier development. Int J Androl 2006;29:241–6; discussion 86–90.
66. Russo VEA, Martienssen RA, Riggs AD, eds. Epigenetic mechanisms of gene regulation. Plainview, NY: Cold Spring Harbor, 1996.
67. Smith CC, Taylor HS. Xenoestrogen exposure imprints expression of genes (Hoxa10) required for normal uterine development. FASEB J 2007;21:239–46.
68. Sharpe RM, Skakkebaek NE. Testicular dysgenesis syndrome: mechanistic insights and potential new downstream effects. Fertil Steril. In press.
69. Skakkebaek NE, Rajpert-De Meyts E, Main KM. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. Hum Reprod 2001;16:972–8.
70. Sharpe RM, Skakkebaek NE. Male reproductive disorders and the role of endocrine disruption: advances in understanding and identification of areas for future research. Pure Appl Chem 2003;75:2023–38.
71. Mylchreest E, Wallace DG, Cattley RC, Foster PM. Dose-dependent alterations in androgen-regulated male reproductive development in rats exposed to Di(n-butyl) phthalate during late gestation. Toxicol Sci 2000;55:143–51.
72. Parks LG, Ostby JS, Lambright CR, Abbott BD, Klinefelter GR, Barlow NJ, et al. The plasticizer diethylhexyl phthalate induces malformations by decreasing fetal testosterone synthesis during sexual differentiation in the male rat. Toxicol Sci 2000;58:339–49.
73. Fisher JS, Macpherson S, Marchetti N, Sharpe RM. Human "testicular dysgenesis syndrome": a possible model using in-utero exposure of the rat to dibutyl phthalate. Hum Reprod 2003;18:1383–94.
74. Mahood IK, Hallmark N, McKinnell C, Walker M, Fisher JS, Sharpe RM. Abnormal Leydig cell aggregation in the fetal testis of rats exposed to di (n-butyl) phthalate and its possible role in testicular dysgenesis. Endocrinology 2005;146:613–23.
75. Scott HM, Hutchison GR, Mahood IK, Hallmark N, Welsh M, De Gendt K, et al. Role of androgens in fetal testis development and dysgenesis. Endocrinology 2007;148:2027–36.
76. Hoei-Hansen CE, Holm M, Rajpert-De Meyts E, Skakkebaek NE. Histological evidence of testicular dysgenesis in contralateral biopsies from 218 patients with testicular germ cell cancer. J Pathol 2003;200:370–4.
77. Nistal M, Gonzalez-Peramato P, Regadera J, Serrano A, Tarin V, De Miguel MP. Primary testicular lesions are associated with testicular germ cell tumors of adult men. Am J Surg Pathol 2006;30:1260–8.
78. Sharpe RM. Pathways of endocrine disruption during male sexual differentiation and masculinization. Best Pract Res Clin Endocrinol Metab 2006;20:91–110.
79. Tan KA, De Gendt K, Atanassova N, Walker M, Sharpe RM, Saunders PT, et al. The role of androgens in sertoli cell proliferation and functional maturation: studies in mice with total or Sertoli cell-selective ablation of the androgen receptor. Endocrinology 2005;146:2674–83.
80. Atanassova NN, Walker M, McKinnell C, Fisher JS, Sharpe RM. Evidence that androgens and oestrogens, as well as follicle-stimulating hormone, can alter Sertoli cell number in the neonatal rat. J Endocrinol 2005;184:107–17.
81. Sharpe RM, McKinnell C, Kivlin C, Fisher JS. Proliferation and functional maturation of Sertoli cells, and their relevance to disorders of testis function in adulthood. Reproduction 2003;125:769–84.
82. Cortes D, Muller J, Skakkebaek NE. Proliferation of Sertoli cells during development of the human testis assessed by stereological methods. Int J Androl 1987;10:589–96.
83. Baskin LS. Can we prevent hypospadias? Fertil Steril. In press.
84. Swan SH, Main KM, Liu F, Stewart SL, Kruse RL, Calafat AM, et al. Decrease in anogenital distance among male infants with prenatal phthalate exposure. Environ Health Perspect 2005;113:1056–61.
85. Prins GS, Tang WY, Belmonte J, Ho SM. Developmental exposure to bisphenol A increases prostate cancer susceptibility in adult rats: epigenetic mode of action is implicated. Fertil Steril. In press.
86. Ho SM, Tang WY, Belmonte de Frausto J, Prins GS. Developmental exposure to estradiol and bisphenol A increases susceptibility to prostate

carcinogenesis and epigenetically regulates phosphodiesterase type 4 variant 4. Cancer Res 2006;66:5624–32.
87. Hauser R, Sokol R. Science linking environmental contaminant exposures with fertility and reproductive health impacts in the adult male. Fertil Steril. In press.
88. Hauser R, Meeker JD, Duty S, Silva MJ, Calafat AM. Altered semen quality in relation to urinary concentrations of phthalate monoester and oxidative metabolites. Epidemiology 2006;17:682–91.
89. Jonsson BA, Richthoff J, Rylander L, Giwercman A, Hagmar L. Urinary phthalate metabolites and biomarkers of reproductive function in young men. Epidemiology 2005;16:487–93.
90. Hsu PC, Huang W, Yau WJ, Wu MH, Guo YL, Lambert GH. Sperm changes in men exposed to polychlorinated biphenyls and dibenzofurans. JAMA 2003;289:2943–4.
91. Guo YL, Hsu PC, Hsu CC, Lambert GH. Semen quality after prenatal exposure to polychlorinated biphenyls and dibenzofurans. Lancet 2000;356:1240–1.
92. Hauser R. The environment and male fertility: recent research on emerging chemicals and semen quality. Semin Reprod Med 2006;24: 156–67.
93. Cunningham M. Chronic occupational lead expnsure: the potential effect on sexual function and reproductive ability in male workers. Aaohn J 1986;34:277–9.
94. Benoff S, Jacob A, Hurley IR. Male infertility and environmental exposure to lead and cadmium. Hum Reprod Update 2000;6:107–21.
95. Telisman S, Cvitkovic P, Jurasovic J, Pizent A, Gavella M, Rocic B. Semen quality and reproductive endocrine function in relation to biomarkers of lead, cadmium, zinc, and copper in men. Environ Health Perspect 2000;108:45–53.
96. Apostoli P, Kiss P, Porru S, Bonde JP, Vanhoorne M. Male reproductive toxicity of lead in animals and humans. ASCLEPIOS Study Group. Occup Environ Med 1998;55:364–74.
97. Lancranjan I, Popescu HI, Gavanescu O, Klepsch I, Serbanescu M. Reproductive ability of workmen occupationally exposed to lead. Arch Environ Health 1975;30:396–401.
98. Winder C. Reproductive and chromosomal effects of occupational exposure to lead in the male. Reprod Toxicol 1989;3:221–33.
99. Sheiner EK, Sheiner E, Hammel RD, Potashnik G, Carel R. Effect of occupational exposures on male fertility: literature review. Ind Health 2003;41:55–62.
100. Figa-Talamanca I, Traina ME, Urbani E. Occupational exposures to metals, solvents and pesticides: recent evidence on male reproductive effects and biological markers. Occup Med (Lond) 2001;51:174–88.
101. Potashnik G, Porath A. Dibromochloropropane (DBCP): a 17-year reassessment of testicular function and reproductive performance. J Occup Environ Med 1995;37:1287–92.
102. Lantz GD, Cunningham GR, Huckins C, Lipshultz LI. Recovery from severe oligospermia after exposure to dibromochloropropane. Fertil Steril 1981;35:46–53.
103. Britt KL, Findlay JK. Estrogen actions in the ovary revisited. J Endocrinol 2002;175:269–76.
104. Palter SF, Tavares AB, Hourvitz A, Veldhuis JD, Adashi EY. Are estrogens of import to primate/human ovarian folliculogenesis? Endocr Rev 2001;22:389–424.
105. Mather JP, Moore A, Li RH. Activins, inhibins, and follistatins: further thoughts on a growing family of regulators. Proc Soc Exp Biol Med 1997;215:209–22.
106. Findlay JK, Drummond AE, Dyson M, Baillie AJ, Robertson DM, Ethier JF. Production and actions of inhibin and activin during folliculogenesis in the rat. Mol Cell Endocrinol 2001;180:139–44.
107. Pangas SA, Rademaker AW, Fishman DA, Woodruff TK. Localization of the activin signal transduction components in normal human ovarian follicles: implications for autocrine and paracrine signaling in the ovary. J Clin Endocrinol Metab 2002;87:2644–57.
108. Ethier JF, Findlay JK. Roles of activin and its signal transduction mechanisms in reproductive tissues. Reproduction 2001;121:567–75.
109. Woodruff TK, Lyon RJ, Hansen SE, Rice GC, Mather JP. Inhibin and activin locally regulate rat ovarian folliculogenesis. Endocrinology 1990;127:3196–205.
110. Xiao S, Robertson DM, Findlay JK. Effects of activin and follicle-stimulating hormone (FSH)-suppressing protein/follistatin on FSH receptors and differentiation of cultured rat granulosa cells. Endocrinology 1992;131:1009–16.
111. Nakamura M, Nakamura K, Igarashi S, Tano M, Miyamoto K, Ibuki Y, et al. Interaction between activin A and cAMP in the induction of FSH receptor in cultured rat granulosa cells. J Endocrinol 1995;147:103–10.
112. Sadatsuki M, Tsutsumi O, Yamada R, Muramatsu M, Taketani Y. Local regulatory effects of activin A and follistatin on meiotic maturation of rat oocytes. Biochem Biophys Res Commun 1993;196:388–95.
113. Ikeda Y, Nagai A, Ikeda MA, Hayashi S. Neonatal estrogen exposure inhibits steroidogenesis in the developing rat ovary. Dev Dyn 2001;221: 443–53.
114. Forsberg JG. Treatment with different antiestrogens in the neonatal period and effects in the cervicovaginal epithelium and ovaries of adult mice: a comparison to estrogen-induced changes. Biol Reprod 1985;32: 427–41.
115. Iguchi T, Fukazawa Y, Uesugi Y, Takasugi N. Polyovular follicles in mouse ovaries exposed neonatally to diethylstilbestrol in vivo and in vitro. Biol Reprod 1990;43:478–84.
116. Iguchi T, Takasugi N, Bern HA, Mills KT. Frequent occurrence of polyovular follicles in ovaries of mice exposed neonatally to diethylstilbestrol. Teratology 1986;34:29–35.
117. Jefferson WN, Couse JF, Padilla-Banks E, Korach KS, Newbold RR. Neonatal exposure to genistein induces estrogen receptor (ER)alpha expression and multioocyte follicles in the maturing mouse ovary: evidence for ERbeta-mediated and nonestrogenic actions. Biol Reprod 2002;67:1285–96.
118. Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. N Engl J Med 1971;284:878–81.
119. Li S, Hansman R, Newbold R, Davis B, McLachlan JA, Barrett JC. Neonatal diethylstilbestrol exposure induces persistent elevation of c-fos expression and hypomethylation in its exon-4 in mouse uterus. Mol Carcinog 2003;38:78–84.
120. Newbold RR, Hanson RB, Jefferson WN. Ontogeny of lactoferrin in the developing mouse uterus: a marker of early hormone response. Biol Reprod 1997;56:1147–57.
121. Newbold RR, Bullock BC, McLachlan JA. Uterine adenocarcinoma in mice following developmental treatment with estrogens: a model for hormonal carcinogenesis. Cancer Res 1990;50:7677–81.
122. Couse JF, Dixon D, Yates M, Moore AB, Ma L, Maas R, et al. Estrogen receptor-alpha knockout mice exhibit resistance to the developmental effects of neonatal diethylstilbestrol exposure on the female reproductive tract. Dev Biol 2001;238:224–38.
123. Mendola P, Messer LC, Rappazzo R. Science linking environmental contaminant exposures with fertility and reproductive health impacts in the adult female. Fertil Steril. In press.
124. Selevan SG, Rice DC, Hogan KA, Euling SY, Pfahles-Hutcheos A, Bethel J. Blood lead concentration and delayed puberty in girls. N Engl J Med 2003;348:1527–36.
125. Wu T, Buck GM, Mendola P. Blood lead levels and sexual maturation in U.S. girls: the Third National Health and Nutrition Examination Survey, 1988–1994. Environ Health Perspect 2003;111:737–41.
126. Denham M, Schell LM, Deane G, Gallo MV, Ravenscroft J, DeCaprio AP. Relationship of lead, mercury, mirex, dichlorodiphenyldichloroethylene, hexachlorobenzene, and polychlorinated biphenyls to timing of menarche among Akwesasne Mohawk girls. Pediatrics 2005;115:e127–34.
127. Colon I, Caro D, Bourdony CJ, Rosario O. Identification of phthalate esters in the serum of young Puerto Rican girls with premature breast development. Environ Health Perspect 2000;108:895–900.
128. Ouyang F, Perry MJ, Venners SA, Cheo C, Wang B, Yang F, et al. Serum DDT, age at menarche, and abnormal menstrual cycle length. Occup Environ Med 2005;62:878–84.
129. Krstevska-Konstantinova M, Charlier C, Craen M, Du Caju M, Heinrichs C, de Beaufort C, et al. Sexual precocity after immigration from developing countries to Belgium: evidence of previous exposure to organochlorine pesticides. Hum Reprod 2001;16:1020–6.

130. Tang N, Zhu ZQ. Adverse reproductive effects in female workers of lead battery plants. Int J Occup Med Environ Health 2003;16: 359–61.
131. Windham GC, Waller K, Anderson M, Fenster L, Mendola P, Swan S. Chlorination by-products in drinking water and menstrual cycle function. Environ Health Perspect 2003;111:935–41; discussion A409.
132. Eskenazi B, Warner M, Mocarelli P, Samuels S, Needham LL, Patterson DG Jr, et al. Serum dioxin concentrations and menstrual cycle characteristics. Am J Epidemiol 2002;156:383–92.
133. Farr SL, Cooper GS, Cai J, Savitz DA, Sandler DP. Pesticide use and menstrual cycle characteristics among premenopausal women in the Agricultural Health Study. Am J Epidemiol 2004;160:1194–204.
134. Cooper GS, Klebanoff MA, Promislow J, Brock JW, Longnecker MP. Polychlorinated biphenyls and menstrual cycle characteristics. Epidemiology 2005;16:191–200.
135. Hsieh GY, Wang JD, Cheng TJ, Chen PC. Prolonged menstrual cycles in female workers exposed to ethylene glycol ethers in the semiconductor manufacturing industry. Occup Environ Med 2005;62:510–6.
136. Wang X, Tian J. Health risks related to residential exposure to cadmium in Zhenhe County, China. Arch Environ Health 2004;59:324–30.
137. Yu ML, Guo YL, Hsu CC, Rogan WJ. Menstruation and reproduction in women with polychlorinated biphenyl (PCB) poisoning: long-term follow-up interviews of the women from the Taiwan Yucheng cohort. Int J Epidemiol 2000;29:672–7.
138. Gerhard I, Frick A, Monga B, Runnebaum B. Pentachlorophenol exposure in women with gynecological and endocrine dysfunction. Environ Res 1999;80:383–8.
139. Perry MJ, Ouyang F, Korrick SA, Venners SA, Chen C, Xu X, et al. A prospective study of serum DDT and progesterone and estrogen levels across the menstrual cycle in nulliparous women of reproductive age. Am J Epidemiol 2006;164:1056–64.
140. Windham GC, Lee D, Mitchell P, Anderson M, Petreas M, Lasley B. Exposure to organochlorine compounds and effects on ovarian function. Epidemiology 2005;16:182–90.
141. Cobellis L, Latini G, De Felice C, Razzi S, Paris I, Ruggieri F, et al. High plasma concentrations of di-(2-ethylhexyl)-phthalate in women with endometriosis. Hum Reprod 2003;18:1512–5.
142. Reddy BS, Rozati R, Reddy BV, Raman NV. Association of phthalate esters with endometriosis in Indian women. BJOG 2006;113:515–20.
143. Chang SH, Cheng BH, Lee SL, Chuang HY, Yang CY, Sung FC, et al. Low blood lead concentration in association with infertility in women. Environ Res 2006;101:380–6.
144. Venners SA, Korrick S, Xu X, Chen C, Guang W, Huang A, et al. Preconception serum DDT and pregnancy loss: a prospective study using a biomarker of pregnancy. Am J Epidemiol 2005;162:709–16.
145. Longnecker MP, Klebanoff MA, Dunson DB, Guo X, Chen Z, Zhou H, et al. Maternal serum level of the DDT metabolite DDE in relation to fetal loss in previous pregnancies. Environ Res 2005;97:127–33.
146. Korrick SA, Chen C, Damokosh AI, Ni J, Liu X, Cho SI, et al. Association of DDT with spontaneous abortion: a case–control study. Ann Epidemiol 2001;11:491–6.
147. Greenlee AR, Arbuckle TE, Chyou PH. Risk factors for female infertility in an agricultural region. Epidemiology 2003;14:429–36.
148. Abell A, Juul S, Bonde JP. Time to pregnancy among female greenhouse workers. Scand J Work Environ Health 2000;26:131–6.
149. Curtis KM, Savitz DA, Weinberg CR, Arbuckle TE. The effect of pesticide exposure on time to pregnancy. Epidemiology 1999;10:112–7.
150. Idruvo AJ, Sanin LH, Cole D, Chavarro J, Caceres H, Narvaez J, et al. Time to first pregnancy among women working in agricultural production. Int Arch Occup Environ Health 2005;78:493–500.
151. Crisostomo L, Molina VV. Pregnancy outcomes among farming households of Nueva Ecija with conventional pesticide use versus integrated pest management. Int J Occup Environ Health 2002;8:232–42.
152. Garry VF, Harkins M, Lyubimov A, Erickson L, Long L. Reproductive outcomes in the women of the Red River Valley of the north. I. The spouses of pesticide applicators: pregnancy loss, age at menarche, and exposures to pesticides. J Toxicol Environ Health A 2002;65:769–86.
153. Arbuckle TE, Savitz DA, Mery LS, Curtis KM. Exposure to phenoxy herbicides and the risk of spontaneous abortion. Epidemiology 1999;10:752–60.
154. Arbuckle TE, Lin Z, Mery LS. An exploratory analysis of the effect of pesticide exposure on the risk of spontaneous abortion in an Ontario farm population. Environ Health Perspect 2001;109:851–7.
155. Bindali BB, Kaliwal BB. Anti-implantation effect of a carbamate fungicide mancozeb in albino mice. Ind Health 2002;40:191–7.
156. Greenlee AR, Ellis TM, Berg RL. Low-dose agrochemicals and lawncare pesticides induce developmental toxicity in murine preimplantation embryos. Environ Health Perspect 2004;112:703–9.
157. Plenge-Bonig A, Karmaus W. Exposure to toluene in the printing industry is associated with subfecundity in women but not in men. Occup Environ Med 1999;56:443–8.
158. Wennborg H, Bodin L, Vainio H, Axelsson G. Solvent use and time to pregnancy among female personnel in biomedical laboratories in Sweden. Occup Environ Med 2001;58:225–31.
159. Sallmen M, Baird DD, Hoppin JA, Blair A, Sandler DP. Fertility and exposure to solvents among families in the Agricultural Health Study. Occup Environ Med 2006;63:469–75.
160. Sugiura-Ogasawara M, Ozaki Y, Sonta S, Makino T, Suzumori K. Exposure to bisphenol A is associated with recurrent miscarriage. Hum Reprod 2005;20:2325–9.
161. Susiarjo M, Hassold TJ, Freeman E, Hunt PA. Bisphenol A exposure in utero disrupts early oogenesis in the mouse. PLoS Genet 2007;3:e5.
162. Hunt PA, Koehler KE, Susiarjo M, Hodges CA, Ilagan A, Voigt RC, et al. Bisphenol a exposure causes meiotic aneuploidy in the female mouse. Curr Biol 2003;13:546–53.
163. Eskenazi B, Warner M, Marks AR, Samuels S, Gerthoux PM, Vercellini P, et al. Serum dioxin concentrations and age at menopause. Environ Health Perspect 2005;113:858–62.
164. Akkina J, Reif J, Keefe T, Bachand A. Age at natural menopause and exposure to organochlorine pesticides in Hispanic women. J Toxicol Environ Health A 2004;67:1407–22.
165. Cooper GS, Savitz DA, Millikan R, Chiu Kit T. Organochlorine exposure and age at natural menopause. Epidemiology 2002;13:729–33.
166. Farr SL, Cai J, Savitz DA, Sandler DP, Hoppin JA, Cooper GS. Pesticide exposure and timing of menopause: the Agricultural Health Study. Am J Epidemiol 2006;163:731–42.
167. Taupeau C, Poupon J, Nome F, Lefevre B. Lead accumulation in the mouse ovary after treatment-induced follicular atresia. Reprod Toxicol 2001;15:385–91.
168. Meirow D, Lewis H, Nugent D, Epstein M. Subclinical depletion of primordial follicular reserve in mice treated with cyclophosphamide: clinical importance and proposed accurate investigative tool. Hum Reprod 1999;14:1903–7.
169. Mayer LP, Pearsall NA, Christian PJ, Devine PJ, Payne CM, McCuskey MK, et al. Long-term effects of ovarian follicular depletion in rats by 4-vinylcyclohexene diepoxide. Reprod Toxicol 2002;16: 775–81.
170. Kao SW, Sipes IG, Hoyer PB. Early effects of ovotoxicity induced by 4-vinylcyclohexene diepoxide in rats and mice. Reprod Toxicol 1999;13: 67–75.
171. Borman SM, Christian PJ, Sipes IG, Hoyer PB. Ovotoxicity in female Fischer rats and B6 mice induced by low-dose exposure to three polycyclic aromatic hydrocarbons: comparison through calculation of an ovotoxic index. Toxicol Appl Pharmacol 2000;167:191–8.
172. Bodensteiner KJ, Sawyer HR, Moeller CL, Kane CM, Pau KY, Klinefelter GR, et al. Chronic exposure to dibromoacetic acid, a water disinfection byproduct, diminishes primordial follicle populations in the rabbit. Toxicol Sci 2004;80:83–91.
173. Baligar PN, Kaliwal BB. Induction of gonadal toxicity to female rats after chronic exposure to mancozeb. Ind Health 2001;39:235–43.
174. Windham G, Fenster L. Environmental contaminants and pregnancy outcomes. Fertil Steril. In press.
175. National Cancer Institute. Health effects of exposure to environmental tobacco smoke: the report of the California Environmental Protection Agency, Smoking and Tobacco Control Monograph No. 10. Bethesda,

MD: US Department of Health and Human Services, National Institutes of Health, 1999.
176. US Department of Health and Human Services. The health consequences of involuntary exposure to tobacco smoke: a report of the Surgeon General. Washington, DC: USDHHS, Public Health Service, Office of the Surgeon General, 2006.
177. Bove F, Shim Y, Zeitz P. Drinking water contaminants and adverse pregnancy outcomes: a review. Environ Health Perspect 2002; 110(Suppl 1):61–74.
178. Nieuwenhuijsen MJ, Toledano MB, Eaton NE, Fawell J, Elliott P. Chlorination disinfection byproducts in water and their association with adverse reproductive outcomes: a review. Occup Environ Med 2000;57: 73–85.
179. Tardiff RG, Carson ML, Ginevan ME. Updated weight of evidence for an association between adverse reproductive and developmental effects and exposure to disinfection by-products. Regul Toxicol Pharmacol 2006;45:185–205.
180. Al-Hiyasat AS, Darmani H, Elbetieha AM. Effects of bisphenol A on adult male mouse fertility. Eur J Oral Sci 2002;110:163–7.
181. Sakaue M, Ohsako S, Ishimura R, Kurosawa S, Kurohmaru M, Hayashi Y, et al. Bisphenol-A affects spermatogenesis in the adult rat even at a low dose. J Occup Health 2001;43:185–90.
182. Howdeshell KL, Hotchkiss AK, Thayer KA, Vandenbergh JG, vom Saal FS. Exposure to bisphenol A advances puberty. Nature 1999;401: 763–4.
183. Timms BG, Howdeshell KL, Barton L, Bradley S, Richter CA, vom Saal FS. Estrogenic chemicals in plastic and oral contraceptives disrupt development of the fetal mouse prostate and urethra. Proc Natl Acad Sci USA 2005;102:7014–9.
184. Gupta C. Reproductive malformation of the male offspring following maternal exposure to estrogenic chemicals. Proc Soc Exp Biol Med 2000;224:61–8.
185. Herath CB, Jin W, Watanabe G, Arai K, Suzuki AK, Taya K. Adverse effects of environmental toxicants, octylphenol and bisphenol A, on male reproductive functions in pubertal rats. Endocrine 2004;25: 163–72.
186. del Rio Gomez I, Marshall T, Tsai P, Shao YS, Guo YL. Number of boys born to men exposed to polychlorinated byphenyls. Lancet 2002;360: 143–4.
187. Sharara FI, Seifer DB, Flaws JA. Environmental toxicants and female reproduction. Fertil Steril 1998;70:613–22.
188. Hruska KS, Furth PA, Seifer DB, Sharara FI, Flaws JA. Environmental factors in infertility. Clin Obstet Gynecol 2000;43:821–9.
189. LaDou J, ed. Occupational and environmental medicine. 3rd ed. Stamford, CT: Lange Medical/McGraw Hill, 2004.
190. Correa A, Gray RH, Cohen R, Rothman N, Shah F, Seacat H, et al. Ethylene glycol ethers and risks of spontaneous abortion and subfertility. Am J Epidemiol 1996;143:707–17.
191. Eskenazi B, Gold EB, Samuels SJ, Wight S, Lasley BL, Hammond SK, et al. Prospective assessment of fecundability of female semiconductor workers. Am J Ind Med 1995;28:817–31.
192. Fuortes L, Clark MK, Kirchner HL, Smith EM. Association between female infertility and agricultural work history. Am J Ind Med 1997; 31:445–51.
193. Schettler T, Solomon G, Valenti M, Huddle A. Generations at risk. Reproductive health and the environment. Cambridge, MA: MIT Press, 1999.
194. Oliva A, Spira A, Multigner L. Contribution of environmental factors to the risk of male infertility. Hum Reprod 2001;16:1768–76.
195. Swan SH, Kruse RL, Liu F, Barr DB, Drobnis EZ, Redmon JB, et al. Semen quality in relation to biomarkers of pesticide exposure. Environ Health Perspect 2003;111:1478–84.
196. Goldsmith JR. Dibromochloropropane: epidemiological findings and current questions. Ann N Y Acad Sci 1997;837:300–6.
197. Savitz DA, Arbuckle T, Kaczor D, Curtis KM. Male pesticide exposure and pregnancy outcome. Am J Epidemiol 1997;146:1025–36.
198. Recio R, Robbins WA, Borja-Aburto V, Moran-Martinez J, Froines JR, Hernandez RM, et al. Organophosphorous pesticide exposure increases the frequency of sperm sex null aneuploidy. Environ Health Perspect 2001;109:1237–40.
199. Sanchez-Pena LC, Reyes BE, Lopez-Carrillo L, Recio R, Moran-Martinez J, Cebrian ME, et al. Organophosphorous pesticide exposure alters sperm chromatin structure in Mexican agricultural workers. Toxicol Appl Pharmacol 2004;196:108–13.
200. Garry VF, Holland SE, Erickson LL, Burroughs BL. Male reproductive hormones and thyroid function in pesticide applicators in the Red River Valley of Minnesota. J Toxicol Environ Health A 2003;66: 965–86.
201. Garry VF, Schreinemachers D, Harkins ME, Griffith J. Pesticide appliers, biocides, and birth defects in rural Minnesota. Environ Health Perspect 1996;104:394–9.
202. Laws SC, Ferrell JM, Stoker TE, Schmid J, Cooper RL. The effects of atrazine on female wistar rats: an evaluation of the protocol for assessing pubertal development and thyroid function. Toxicol Sci 2000;58: 366–76.
203. Monosson E, Kelce WR, Lambright C, Ostby J, Gray LE Jr. Peripubertal exposure to the antiandrogenic fungicide, vinclozolin, delays puberty, inhibits the development of androgen-dependent tissues, and alters androgen receptor function in the male rat. Toxicol Ind Health 1999;15:65–79.
204. Stoker TE, Guidici DL, Laws SC, Cooper RL. The effects of atrazine metabolites on puberty and thyroid function in the male Wistar rat. Toxicol Sci 2002;67:198–206.
205. Kristensen P, Irgens LM, Andersen A, Bye AS, Sundheim L. Birth defects among offspring of Norwegian farmers, 1967–1991. Epidemiology 1997;8:537–44.
206. Fisher JS. Environmental anti-androgens and male reproductive health: focus on phthalates and testicular dysgenesis syndrome. Reproduction 2004;127:305–15.
207. Gray LE, Ostby J, Furr J, Wolf CJ, Lambright C, Parks L, et al. Effects of environmental antiandrogens on reproductive development in experimental animals. Hum Reprod Update 2001;7:248–64.
208. Anway MD, Cupp AS, Uzumcu M, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science 2005;308:1466–9.
209. Whyatt RM, Rauh V, Barr DB, Camann DE, Andrews HF, Garfinkel R, et al. Prenatal insecticide exposures and birth weight and length among an urban minority cohort. Environ Health Perspect 2004;112: 1125–32.
210. Perera FP, Rauh V, Tsai WY, Kinney P, Camann D, Barr D, et al. Effects of transplacental exposure to environmental pollutants on birth outcomes in a multiethnic population. Environ Health Perspect 2003;111: 201–5.
211. Levario-Carrillo M, Amato D, Ostrosky-Wegman P, Gonzalez-Horta C, Corona Y, Sanin LH. Relation between pesticide exposure and intrauterine growth retardation. Chemosphere 2004;55:1421–7.
212. Duty SM, Silva MJ, Barr DB, Brock JW, Ryan L, Chen Z, et al. Phthalate exposure and human semen parameters. Epidemiology 2003;14: 269–77.
213. Lovekamp-Swan T, Davis BJ. Mechanisms of phthalate ester toxicity in the female reproductive system. Environ Health Perspect 2003;111: 139–45.
214. Couse JF, Korach KS. Estrogen receptor-alpha mediates the detrimental effects of neonatal diethylstilbestrol (DES) exposure in the murine reproductive tract. Toxicology 2004;205:55–63.
215. Gray LE Jr, Ostby J, Furr J, Price M, Veeramachaneni DN, Parks L. Perinatal exposure to the phthalates di(2-ethylhexyl)phthalate, BBP, and DINP, but not DEP, DMP, or DOTP, alters sexual differentiation of the male rat. Toxicol Sci 2000;58:350–65.
216. Svensson BG, Nise G, Erfurth EM, Nilsson A, Skerfving S. Hormone status in occupational toluene exposure. Am J Ind Med 1992;22: 99–107.
217. Winker R, Rudiger HW. Reproductive toxicology in occupational settings: an update. Int Arch Occup Environ Health 2006;79:1–10.
218. Ichihara G. Neuro-reproductive toxicities of 1-bromopropane and 2-bromopropane. Int Arch Occup Environ Health 2005;78:79–96.

219. Younglai EV, Holloway AC, Foster WG. Environmental and occupational factors affecting fertility and IVF success. Hum Reprod Update 2005;11:43–57.
220. Sallmen M, Lindbohm ML, Kyyronen P, Nykyri E, Anttila A, Taskinen H, et al. Reduced fertility among women exposed to organic solvents. Am J Ind Med 1995;27:699–713.
221. Beliles RP. Concordance across species in the reproductive and developmental toxicity of tetrachloroethylene. Toxicol Ind Health 2002;18: 91–106.
222. Eskenazi B, Wyrobek AJ, Fenster L, Katz DF, Sadler M, Lee J, et al. A study of the effect of perchloroethylene exposure on semen quality in dry cleaning workers. Am J Ind Med 1991;20:575–91.
223. Kyyronen P, Taskinen H, Lindbohm ML, Hemminki K, Heinonen OP. Spontaneous abortions and congenital malformations among women exposed to tetrachloroethylene in dry cleaning. J Epidemiol Community Health 1989;43:346–51.
224. Vine MF. Smoking and male reproduction: a review. Int J Androl 1996;19:323–37.
225. US Department of Health and Human Seurvices. Women and smoking: a report of the Surgeon General. Washington, DC: US Departtnent of Health and Human Services, Public Health Service, Office of the Surgeon General, 2001.
226. Jensen TK, Jorgensen N, Punab M, Haugen TB, Suominen J, Zilaitiene B, et al. Association of in utero exposure to maternal smoking with reduced semen quality and testis size in adulthood: a cross-sectional study of 1,770 young men from the general population in five European countries. Am J Epidemiol 2004;159:49–58.
227. Miller KP, Borgeest C, Greenfeld C, Tomic D, Flaws JA. In utero effects of chemicals on reproductive tissues in females. Toxicol Appl Pharmacol 2004;198:111–31.
228. Storgaard L, Bonde JP, Ernst E, Spano M, Andersen CY, Frydenberg M, et al. Does smoking during pregnancy affect sons' sperm counts? Epidemiology 2003;14:278–86.
229. Lau C, Butenhoff JL, Rogers JM. The developmental toxicity of perfluoroalkyl acids and their derivatives. Toxicol Appl Pharmacol 2004; 198:231–41.
230. Butenhoff JL, Kennedy GL Jr, Frame SR, O'Connor JC, York RG. The reproductive toxicology of ammonium perfluorooctanoate (APFO) in the rat. Toxicology 2004;196:95–116.
231. Luebker DJ, Case MT, York RG, Moore JA, Hansen KJ, Butenhoff JL. Two-generation reprodnction and cross-foster studies of perfluorooctanesulfonate (PFOS) in rats. Toxicology 2005;215:126–48.
232. Kuriyama SN, Talsness CE, Grote K, Chahoud I. Developmental exposure to low dose PBDE 99: effects on male fertility and neurobehavior in rat offspring. Environ Health Perspect 2005;113:149–54.
233. Sharpe RM, Fisher JS, Millar MM, Jobling S, Sumpter JP. Gestational and lactational exposure of rats to xenoestrogens results in reduced testicular size and sperm production. Environ Health Perspect 1995;103: 1136–43.
234. Sweeney T, Nicol L, Roche JF, Brooks AN. Maternal exposure to octylphenol suppresses ovine fetal follicle-stimulating hormone secretion, testis size, and sertoli cell number. Endocrinology 2000;141: 2667–73.
235. Bogh IB, Christensen P, Dantzer V, Groot M, Thofner IC, Rasmussen RK, et al. Endocrine disrupting compounds: effect of octylphenol on reproduction over three generations. Theriogenology 2001; 55:131–50.
236. Toft G, Hagmar L, Giwercman A, Bonde JP. Epidemiological evidence on reproductive effects of persistent organochlorines in humans. Reprod Toxicol 2004;19:5–26.
237. Buck Louis GM, Weinter JM, Whitcomb BW, Sperrazza R, Schisterman EF, Lobdell DT, et al. Environmental polychlorinated biphenyl exposure and risk of endometriosis. Obstet Gynecol Surv 2005;60:243–4.
238. Eskenazi B, Mocarelli P, Warner M, Samuels S, Vercellini P, Olive D, et al. Serum dioxin concentrations and endometriosis: a cohort study in Seveso, Italy. Environ Health Perspect 2002;110:629–34.
239. Rogan WJ, Chen A. Health risks and benefits of bis(4-chlorophenyl)-1,1,1-trichloroethane (DDT). Lancet 2005;366:763–73.
240. Hauser R, Chen Z, Pothier L, Ryan L, Altshul L. The relationship between human semen parameters and environmental exposure to polychlorinated biphenyls and p,p'-DDE. Environ Health Perspect 2003; 111:1505–11.
241. Den Hond E, Roels HA, Hoppenbrouwers K, Nawrot T, Thijs L, Vandermeulen C, et al. Sexual maturation in relation to polychlorinated aromatic hydrocarbons: Sharpe and Skakkebaek's hypothesis revisited. Environ Health Perspect 2002;110:771–6.
242. Axmon A. Menarche in women with high exposure to persistent organochlorine pollutants in utero and during childhood. Environ Res 2006; 102:77–82.
243. Wolf CJ, Ostby JS, Gray LE Jr. Gestational exposure to 2,3,7,8-tetrachlorodibenzu-p-dioxin (TCDD) severely alters reproductive function of female hamster offspring. Toxicol Sci 1999;51:259–64.
244. Hosie S, Loff S, Witt K, Niessen K, Waag KL. Is there a correlation between organochlorine compounds and undescended testes? Eur J Pediatr Surg 2000;10:304–9.
245. Hamm JT, Chen CY, Birnbaum LS. A mixture of dioxins, furans, and non-ortho PCBs based upon consensus toxic equivalency factors produces dioxin-like reproductive effects. Toxicol Sci 2003;74:182–91.
246. Ryan JJ, Amirova Z, Carrier G. Sex ratios of children of Russian pesticide producers exposed to dioxin. Environ Health Perspect 2002;110: A699–701.
247. Cohn BA, Cirillo PM, Wolff MS, Schwingl PJ, Cohen RD, Sholtz RI, et al. DDT and DDE exposure in mothers and time to pregnancy in daughters. Lancet 2003;361:2205–6.
248. Klaassen CD, ed. Casarett and Doull's toxicology: the basic science of poisons. 6th ed. New York: McGraw Hill, 2001.
249. Sallmen M, Anttila A, Lindbohm ML, Kyyronen P, Taskinen H, Hemminki K. Time to pregnancy among women occupationally exposed to lead. J Occup Environ Med 1995;37:931–4.
250. Choy CM, Lam CW, Cheung LT, Briton-Jones CM, Cheung LP, Haines CJ. Infertility, blood mercury concentrations and dietary seafood consumption: a case–control study. BJOG 2002;109:1121–5.
251. Jurasovic J, Cvitkovic P, Pizent A, Colak B, Telisman S. Semen quality and reproductive endocrine function with regard to blood cadmium in Croatian male subjects. Biometals 2004;17:735–43.
252. Bonde JP, Joffe M, Apostoli P, Dale A, Kiss P, Spano M, et al. Sperm count and chromatin structure in men exposed to inorganic lead: lowest adverse effect levels. Occup Environ Med 2002;59:234–42.
253. Louis RH. Environmental Influences on female reproductive health. Presentation to the Association of Reproductive Health Professionals, 2005.
254. CHE. CHE Toxicant and Disease Database. Collaborative on Health and the Environment. Available at: http://database.healthhandenvironment.org. Accessed 16 October 2007.

RESPONSES BY HON. JAMES GULLIFORD TO ADDITIONAL QUESTIONS FROM SENATOR BOXER

Question 1. Dr. Giudice. please describe how sensitive the human reproductive and other hormone controlled systems can be to toxic chemicals during periods of particular vulnerability, such as pregnancy or when infants are rapidly developing in the first few years after birth?

Response. Critical and sensitive windows occur periconceptually (prior to, during and shortly after the fertilization of the egg) and during pregnancy; infancy, childhood and puberty (Woodruff et al. 2008). A critical window of susceptibility is a time-sensitive interval during development when exposures to environmental contaminants can disrupt or interfere with the physiology of a cell, tissue or organ (Louis In Press; Morford et a!. 2004). It is a period characterized by marked cellular proliferation and development and numerous changing metabolic capabilities in the developing organism (Calabrese 1986; Louis In Press). Exposures to environmental contaminants during this window may result in adverse, permanent and irreversible effects that can have lifelong and even intergenerational impacts on health. Researchers have suggested the need to also define sensitive windows of susceptibility. Exposures during sensitive windows of susceptibility may still affect development or result in eventual adult disease, but with reduced magnitude compared to the effect of exposure during the critical window of susceptibility (Ben-Shlomo and Kuh 2002; Louis In Press). For example, diethylstilbestrol (DES) exposure reprograms the expression of estrogen responsive genes in Eker rats exposed on post-natal days 3–5 or 10–12 (critical window of susceptibility). leading to increased incidence of uterine leiomyoma. In contrast, rats exposed on post-natal days 17–19 (sensitive window of susceptibility) did not experience this developmental programming and had a rate of uterine leiomyoma that was elevated but not statistically different from control animals (Cook et al. 2007).

THE DES EXAMPLE

Prenatal exposure to DES, a synthetic estrogen and thus an endocrine disrupting chemical (EDC), provides an unfortunate example of the influence of exposure to an endocrine disrupting compound during a critical window development. DES was given to U.S. pregnant women between 1938 and 1971 under the erroneous assumption that it would prevent pregnancy complications. In fact, in utero exposure to DES alters the normal programming of gene families, such as Hox and Wnt, that play important roles in reproductive tract differentiation (Miller et al. 1998; Pavlova et al. 1994; Taylor et al. 1997; Woodruff and Walker In Press).

As a result, female offspring exposed to DES in utero are at increased risk of clear cell adenocarcinoma of the vagina and cervix, structural reproductive tract anomalies, infertility and poor pregnancy outcomes, while male offspring have an increased incidence of genital abnormalities and a possibly increased risk of proState and testicular cancer (Schrager and Potter 2004). These observed human effects have been confirmed in numerous animal models which have also provided information on the toxic mechanisms of DES. Animal experiments have also predicted changes later found in DES-exposed humans. such as oviductal malformations (Newbold et al. 1983), increased incidence of uterine fibroids (Baird and Newbold 2005; Cook et al. 2005; McLachlan et al. 1980) and second— generational effects (Newbold et al. 1998, 2000) such as increased menstrual irregularities (Titus-Ernstoff et al. 2006) and ovarian cancer (Blatt et al. 2003) in DES-granddaughters and increased hypospadias in DES-grandsons (Brouwers et a!. 2006; Klip et a!. 2002).

DES is but one example of how exposure to EDCs can disrupt developing organ systems and cause abnormalities that only appear much later in life or in the subsequent generation (Colborn et al. 1996). Other examples include: prenatal exposure to bisphenol a, an estrogenic chemical, in mice resulted in effects on the daughters developing eggs (Susiarjo and Hunt In Press), and prenatal exposure to phthalates, an anti-androgenic chemical, can result in adverse effects on male reoproductive development such as poor sperm quality and increased incidence of cryptorchidism (undescended testis) and hypospadias (abnormal penis development) (Woodruff et at, under review).

Question 2. Dr. Giudice. could you please explain the importance of considering human exposures to multiple chemicals on very delicate biological systems. like the human endocrine system?

Humans are exposed daily to a mixture of environmental contaminants in air, water and food. In a recent biomonitoring study of over 150 contaminants, the U.S. Centers for Disease Control and Prevention (CDC) reported that all 150 chemicals

were detected in some portion of the U.S. population and that several of the chemicals, such environmental tobacco smoke, lead, mercury and phthalates, are detected in nearly all or all of the population (CDC 2005). These and similar biomonitoring efforts improve our understanding of current body burdens of environmental contaminants. With this knowledge comes a need for better science on the health risks associated with current patterns of exposure, including increased risks resulting from exposures to multiple chemicals. For example, the majority of studies and regulatory focus have been on exposures to individual phthalates, which may underestimate the actual risks. Over 95 percent of the population from ages 6 and to over 65 years is exposed to at least 5 phthalates on a regular basis (Silva et at 2004). Certain phthalates can inhibit testosterone synthesis, thus decreasing testosterone levels. Reducing testosterone levels in rats during in utero development can results in adverse effects on male reproductive development including decreased sperm counts, decreased ano-genital distance, hypospadias, cryptorchidism, and decreased size or agenesis of the accessory sex glands (Woodruff et aI., under review). The severity of effects increases with the dose.

Recent studies show exposure to mixtures of chemicals that can reduce testosterone levels can have dose-additive effects. Rats exposed to a mixture of pesticides that can decrease testosterone levels, vinclozolin, procymidone, and f1utamide, at doses that would not have caused hypospadias alone, resulted in over 50 percent of animals with hypospadias (Christiansen et al. 2008). Another study found prenatal exposure to a mixture of seven phthalates and pesticides produced cumulative, dose additive outcomes in the androgen-dependent tissues (Rider et al. 2008).

A study of the thyroid system has found similar results. A study of a mixture of 18 thyroid disrupting chemicals (dioxins, dibenzofurans and PCBs) was tested at doses comparable to human exposure levels for effects on thyroid hormone levels in rats. The mixture had a dose-additive effect on thyroid hormone levels at environmentally relevant doses and a 2–3 fold greater than dose-additive effect at higher doses (Crofton et al. 2005).

The studies show that chemicals acting on the same system can have cumulative effects. Assessments considering single chemicals in isolation are therefore likely to underestimate the potential effects from real-world exposure to chemical mixtures (Woodruff et aI., under review).

Finally. biomonitoring data indicate that more effort is needed toward approaches that identify and mitigate exposure to harmful chemicals prior to measuring these contaminants in people.

Question 3. Dr. Giudice. as a public health professional and scientist. how important is transparency in ensuring a valid and strong scientific process?

Response. To make informed decisions. it is critical we have the best science available to inform what we know and what we do not know about how environmental chemicals can influence health. Science is an iterative process, as scientific inquiry moves forward, further insights are gained and new questions arise. Capturing and translating the complexities of the science is an ongoing challenge in the regulatory and policy arena. While science pursues new areas of inquiry, decision making requires timely answers to questions about risks and hazards to public health in order to mitigate future or current potential harm (Woodruff et aI., under review). Regulatory context also requires a different sufficiency of evidence. For example, it is not necessary to identify every mechanistic step leading from exposure to outcome to make decisions that consider public health. For example, regulatory decisions are often made based on evidence that a chemical is "likely" to cause a particular outcome, such as cancer. Transparency is an important part of the scientific process—it allows full evaluation of the methods and protocols used from which conclusions are drawn. Without transparency, we cannot fully evaluate the findings from studies nor the conclusions, and this limits our ability to make informed decisions.

Question 4. Dr. Giudice. at the hearing. another witness raised questions about some of the data you relied upon in your testimony. Would you please elaborate on the scientific information you relied upon in your statements. with citations to the literature?

Response. In the beginning of my testimony, I referred to some concerning trends in reproductive health. The sentence and references are below: Compared to 30 years ago, over 25 percent more women get breast cancer (NCI 2004), over 45 percent more men get testicular cancer (Bray et al. 2006; Sokoloff et al. 2007), and 76 percent more men get proState cancer (Penson and Chan 2007).

Senator BOXER. Thank you very much, Doctor.

Our next majority witness is Annette Gellert, Co-Founder and Chair of WELL Network. Welcome.

STATEMENT OF ANNETTE GELLERT, CO-FOUNDER, CHAIR, WELL NETWORK

Ms. GELLERT. Good morning, Chairman Boxer, members of the Committee. Thank you for this opportunity to testify.

My name is Annette Gellert. I am a wife and the mother of three children. I am a Founder of the WELL Network, which promotes green planning, a comprehensive process between industry, government, scientists and informed citizens to solve together environmental health problems.

I am also Chairman of Resource Renewal Institute, whose Green Plan Center researches advanced environmental management strategies.

After a bill was introduced in California concerning biomonitoring, I wanted to know what potentially toxic chemicals might be inside my family. My family and I had our blood tested in 2006 by the Environmental Working Group to determine possible exposure to 70 toxic chemicals. I was alarmed to find out that I had 36 chemicals in my body and shocked that my 16 year old daughter, Heather, had 34 chemicals in hers. There were similar results in the rest of the family. Heather has been on the planet for such a short time, yet she lives in a much more toxic environment.

Of the chemicals that were found in our bodies, some have already been restricted in the European Union. These chemicals are suspected of being harmful to the thyroid, as well as reproductive and neurological systems. I am worried about my children's health. I am worried about my children's ability to reproduce. I am worried about the health of their children, our grandchildren. I am not alone.

I will do everything in my power to protect my children and I am here to ask you to do the same. I am a reproductive cancer survivor, cancer of the placenta is what I had. Too many of my friends are fighting cancer. While I was preparing for this hearing, I got very bad news. My husband, Fred, was diagnosed with bladder cancer. We are going through that now.

A known cause of bladder cancer is industrial chemical exposure. No doubt many of you in this room have similar stories. The cancer rate keeps going up.

There is mounting evidence that numerous chemicals in our environment are seen as contributors to illness. Some of them are known carcinogens. When my children needed Tylenol in school, it required my written permission. When they are exposed to chemicals, it happens without my permission and without my knowledge.

We come into contact with toxic chemicals all the time, from cosmetics to electronics to cleaning agents to plastic containers to children's toys to baby bottles and teethers. We are exposed to harmful chemicals in every aspect of our lives. We have had no choice in our past exposures and continue to have little choice now.

Only a very small percentage of chemicals have been tested for toxicity. We are in a crisis. America needs a new approach, a proven, better way, green planning. The key to progress is building trust that promotes cooperation between sectors, Government, industry, science and an informed public. This strategy is working very well in other countries, where it has been in action for nearly 20 years, creating environmental and economic success.

And now the EU has introduced REACH, a new integrative chemicals policy which is already having an effect, setting the terms for global markets and manufacturing and market access. We are not scientists or chemists. Our concerns represent millions of other women who fear the impact of products we use daily. There is virtually no information we can trust on whether products are safe or not. We need to make those decisions by ourselves.

There is no American scientific body that has assessed all chemicals in common use to determine their impact on human health and no place to get that information. We are greatly concerned that by falling behind other countries' regulations, the United States will become the dumping ground for all the products that cannot be sold in Europe. Because their regulations are stricter than ours.

In the United States, we must prove harm before a product is removed. In Europe, industry must prove safety before a chemical is introduced. We urge you to protect us and start this process by looking at chemicals in a comprehensive way. It is the right thing to do.

Thank you.

[The prepared statement of Ms. Gellert follows:]

Testimony of Annette Gellert
U.S. Senate Committee on Environment and Public Works
on
"Oversight on EPA Toxic Chemical Policies"
Tuesday, April 29, 2008

Senator Barbara Boxer, Chairman
Senator James M. Inhofe, Ranking Member
Dirksen Senate Office Building, Washington, DC

Good morning, Chairman Boxer, Senator Inhofe, and other members of the committee. Thank you for this opportunity to testify on the need for better oversight of toxic chemicals in our country.

My name is Annette Gellert. I am a wife and the mother of three children. I run a charitable foundation and a family business with my husband, Fred.

I am the **founder of WELL Network**, which promotes green planning, a cooperative process between government, industry, and informed citizens to solve environmental health problems comprehensively.

I am also **chair of the board of Resource Renewal Institute,** whose Green Plan Center researches the most advanced environmental management strategies in the world.

I am going to talk about 3 things:

1) Concern for the health of future generations

2) Green planning and green chemistry

3) Hope for United States leadership on comprehensive chemicals policy

After a bill was introduced in the California legislature concerning bio-monitoring, I wanted to know what potentially toxic chemicals might be present in each of my family members. My husband, daughter, two sons, and I had our blood and urine tested in 2006 to determine exposure to 70 chemicals.

I was alarmed to learn that I had 36 of these chemicals in my body, and shocked that my 16 year-old daughter, Heather, had 34 chemicals in her body. Heather has been on the

planet for a lot shorter time than I have, yet she lives in a much more toxic environment.. Heather's exposure to man-made chemicals began with me. I passed on chemicals from my own body to hers through the placenta and in breast milk.

Of the chemicals that were found in our bodies, some have already been restricted in the European Union. These chemicals are suspected to be harmful to thyroid function and reproductive and neurological systems. They are found in the umbilical cord blood of newborn babies. [1]

I am worried about my family's health.. I am worried about my children's ability to have children without complications. I am worried about the health of their generation's offspring—our grandchildren. And I am not alone.

There is mounting evidence that numerous chemicals in our environment are contributing to illness. Some of them are known carcinogens. I am a cancer survivor and my husband is battling bladder cancer now. We, like millions of Americans, had no idea we were being exposed to chemicals that might have contributed to these conditions. We had and continue to have no choice in the matter.

When my kids needed medicine in school, I had to give written permission for them to get it. We do not have such protection when it comes to chemicals routinely used in millions of products and used by hundreds of millions of people.

New chemicals that have been introduced since 1981 when the Toxic Substance Control Act (TSCA) was implemented, are subject to rudimentary screening by EPA before they go on the market. But 90% of chemical substances produced and used today were grandfathered in, as of 1981. Many pre-TSCA chemicals come into contact with the human body daily—from fertilizers, to cookware, to cosmetics, to electronics, to cleaning agents, to food, to water in plastic bottles. These chemicals are in toys, baby bottles, teethers, plastic food containers, home furnishings, and building materials. We are exposed to chemical substances in every aspect of our environment and lives.

I share with every family in the country the concern of not knowing what is safe. The information we need is largely unavailable for the majority of products in the marketplace.

This is why I, representing WELL Network, am here today.

There are many women, in California and around the nation that are dedicating our collective efforts to bring a more integrated, transparent approach to managing chemical exposure in the United States. What is referred to as "green planning" is a long-term, multi-sector process of environmental management that relates to health, society, and economy. We recognize that it is only through cooperation and compromise among industry, government, and the public that we can start to solve the complex problems that threaten our family's and nation's health.

Our current system of protecting the public from toxic exposure is one of confrontation and litigation. A truly comprehensive policy for chemical safety is what we need to protect our nation's health.

We can do this, and better. American business leaders need to be given the incentives to change. That could happen soon in California, through California EPA's Green Chemistry Initiative, which offers promise of a new approach to chemicals policy that will protect public health and make the U.S. competitive and innovative in the design of safer chemicals and products. The Green Chemistry initiative was spurred by the 2008 University of California report to the California EPA, "Green Chemistry: Cornerstone to a Sustainable California," which was signed by more than 125 professors from throughout the UC system. In the report, and an earlier UC report on green chemistry commissioned by the California Legislature, research shows that we need to close the data gap, the safety gap, and the technology gap in the U.S. chemicals market—and we have the ability to do that now. [2]

Several nations have successfully undertaken a systematic assessment of chemicals to which we are routinely exposed, and which are suspected of causing damage to health and the environment. They are using green planning as a framework for protecting the environment and public health.

Most notably, the European Union has adopted the Regulation, Evaluation, and Authorization of Chemicals Act (REACH). REACH requires that 65,000 chemicals grandfathered into use in the EU—and in the U.S.—be submitted for the first time to an assessment of their toxicity. Other chemicals that are known endocrine disrupters, for instance, are being taken out of toys and cosmetics now, and out of circulation. This is a huge step toward public safety, as the EU represents 450 million people across 27 countries. [3]

It is chemical policies like REACH that are setting the terms for global markets in manufacturing, distribution, and market access—markets that are closing to American business because our products contain toxics restricted or banned elsewhere. Our chemical industries have to change to keep up, and need the incentives and oversight from government to do so.

Every report I've read, including those from the GAO, says that the Toxic Substance Control Act has fostered a weak chemical product regulatory system, despite the good intentions of its authors thirty years ago. It is weak because it doesn't give government the power to effectively regulate the potential hazards to our health. And TSCA does nothing to encourage innovation of alternatives by industry.

WELL Network members are not scientists or chemists. We are women in business, philanthropy, and civic engagement. Our concerns represent millions of other women who want to be responsible purchasers of the products our families use. Our awareness is high, but we can't memorize the relative toxicity of the tens of thousands of chemicals in the products we use. To make smart choices, we need our personal efforts to be matched

by an intelligent, functioning government agency that knows which chemicals are safe and which are not. And we need our government to have the authority to use sticks and carrots to keep the more dangerous chemicals off store shelves and out of our and our children's bodies.

The U.S. can do better. Through REACH and other directives, EU regulators are demanding disclosure on chemical substances by industry. Honoring propriety concerns while providing transparency and accountability, industry has already started to produce new, better, and safer chemicals.

In surveys conducted for the European Union on the actual effect of environmental policy compliance by companies, it was found that the higher costs anticipated were overly exaggerated. It was also found that these same environmental policies prompted hundreds of millions of euros in new green investments.[4]

The predicted dire consequences to the competitive position of EU companies in the world didn't happen either. Those same companies are not losing but increasing their competitive edge over American companies globally. We are greatly concerned that the U.S. is becoming the dumping ground for all the products that cannot be sold elsewhere in the world. We need to put the EPA in a credible position to decide what is or is not healthy for American citizens.

Finally, consider a future where legions of American women—women like me who buy these products for our children and families, and invest in these companies—decide we can't trust that the EPA has the authority to assure the safety of American products. In this future scenario, we will buy and invest in European products. Whether you agree, or industry agrees that those products are safer won't be relevant to our buying decisions. I don't want that second class future for my country, and neither do our leaders.

We can't do it overnight, but we have to begin.

We want the United States to set the standard for a healthy environment and a healthy nation. I owe that to my daughter and sons, and you owe it to your children and grandchildren as well.

Thank you.

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Background information on Ms. Gellert's affiliations:

WELL Network is a nonprofit, non-partisan organization. Our members include women who are business leaders, professionals, philanthropists, and decision-makers within their communities. We formed WELL Network in 2003 to bring attention to shortsighted and poorly coordinated policies that have enabled pollution, toxic chemicals, and global warming to put the health of our families at risk.

Through symposia, workshops, and publications we have been educating and mobilizing our friends, associates, and political leaders about solutions to serious health and environmental problems. These include the presence of potentially harmful chemicals in our bodies from everyday products, the impacts of air pollution on our families' health, and the immense challenges of climate change to our children and grandchildren. For information please visit. http://www.wellnetwork.org To restore California's environmental health, we offer support and comprehensive solutions to business leaders and policymakers. We are expanding our network of informed, effective, and engaged women to move these goals forward.

The **Resource Renewal Institute** (RRI) facilitates the creation, development, and implementation of practical strategies to solve the entire complex environmental problem by addressing it comprehensively. RRI is an incubator of transformational ideas designed to challenge and change the piecemeal way our resources are currently managed and protected. RRI advocates for implementing long-term policies and action plans, such as green planning, which will guarantee the health of the planet and a high quality of life in the future.

Green planning is sustainability in action. Countries around the world are proving that environmental sustainability and economic vitality are not mutually exclusive. Through a shared vision and cooperative effort among all sectors of society, these nations are demonstrating that a healthy environment, enhanced quality of life, and a vibrant economy not only can exist, they must coexist to remain viable over time. Information on green planning can be found at http://www.rri.org.

References

1. Environmental Working Group. "Body Burden: the Pollution in People." http://www.ewg.org/reports/bodyburden

2. Michael P. Wilson, Ph.D., and Megan R. Schwarzman, MD, Ph.D., School of Public Health, UC Berkeley. "Green Chemistry: Cornerstone to a Sustainable California," (UC Centers for Occupational and Environmental Health. http://coeh.berkeley.edu/greenchemistry.htm

3. Mark Schapiro. *Exposed: The Toxic Chemistry of Everyday Products and What's at Stake for American Power."* (Vermont: Chelsea Green Publishing Company, 2007).

4. "Sectoral Costs of Environmental Policy" final report, European Commission, Directorate General Environment, VITO, December 2007

Executive Summary

Taking it to the States

A Call for Action on Comprehensive Chemicals Policy Development

A Green Plan Approach

A report by Eric Siy
Commissioned by WELL Network

Executive Summary

In this era of high-speed access to seemingly endless information, it is almost inconceivable how little is known about the health and environmental effects of the chemicals that have come to define how people live. As ingredients in the millions of products manufactured, sold, used and consumed every day, many of these chemicals may have a far greater impact on illness and mortality than we have realized.

This report calls for action in California and New York to drive innovation in creating a chemicals policy that protects human health and the environment, by applying lessons of the European Union where significant strides have been made. Enabling Europe's progress are its deep societal commitments to sustainable development—enshrined in treaty, statute and draft constitution, and explicitly referenced as the "overriding goal" of the EU's new chemical policy, "REACH" (Registration, Evaluation and Authorization of Chemicals). While yet to be enacted, REACH represents the most integrated, practical approach to "ensure a high level of protection for human health and the environment, while ensuring the efficient functioning of the internal market, and stimulating innovation and competitiveness in the chemicals industry."[1]

REACH also results from a sweeping environmental policy process that first emerged in EU member states pursuing sustainable development. The National Environmental Policy Plan of the Netherlands (NEPP), adopted in 1989, offers the earliest and best-known example of what is commonly called a "green plan"—a deliberate strategy for realizing the economic, environmental and social goals of sustainability.

10 Characteristics of Green Plans

[illegible]

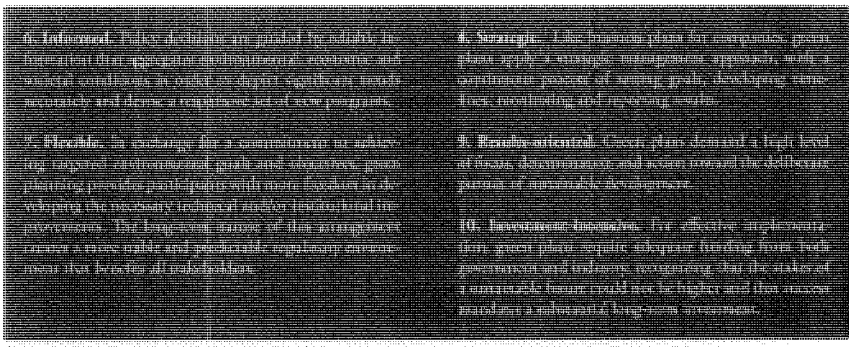
1. Long term. [illegible]

2. Comprehensive. [illegible]

3. Dynamic. [illegible]

4. Cooperative. [illegible]

5. Integrated. [illegible]



Green plans are being developed in response to the failure of conventional policies to prevent environmental decline. They are comprehensive and integrated strategies that establish a necessary framework for the intentional pursuit of sustainable development. The green plan approach of the Netherlands has influenced policy developments in other EU member states and the European Union as a whole. Integral to the Dutch green plan are extensive provisions for chemicals reform.

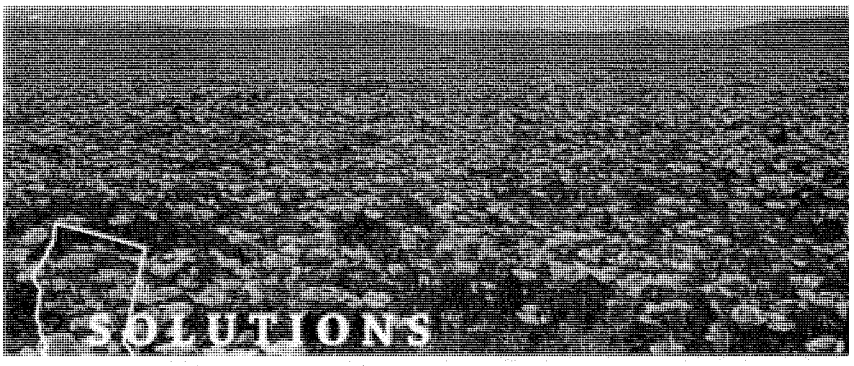
The ambitious aims of REACH are now achievable in the EU because of the larger context provided by the green plan model as presented in the Fifth EU Environment Action Programme, "Towards Sustainability," adopted in 1993.

The United States and Europe—the world's two largest chemical manufacturers—face strikingly similar problems on chemicals and other environmental priorities, yet their current responses stand in sharp contrast.

The United States and Europe—the world's two largest chemical producing nations—face strikingly similar problems with chemicals and other environmental priorities, yet their current responses stand in sharp contrast. Through this call to action, WELL Network is planting the seeds for changing a flawed US system that is failing to protect human health and the environment from the hazards and risks posed by chemicals, and failing to provide for the possibility of a sustainable future.

The process leading to the development of REACH offers a working model for establishing a similarly ambitious program in the United States. Just as progressive EU member states supplied the necessary vision and leadership for sustainable development to become the driving ambition of the entire European Union, progressive US states could lead the way toward a new system of protections with the same essential purpose. The strides already made by Europe can accelerate this process in the US.

This report calls for a positive course of action that brings together stakeholders in California and New York. As has been often demonstrated in the past, the leadership of these two states can have a significant ripple effect on the rest of the country. The actions proposed in this report are meant to capitalize on this record. A key objective will be to foster coordination and cross-fertilization of initiatives between the two states by strengthening linkages among advocates and decision makers. The goal is to generate sustained momentum toward chemicals policy reforms that, as in Europe, are intended to help move the US closer to sustainable development—meeting today's needs without compromising the promise of tomorrow.



Although some leading businesses have adopted sustainable practices, the vast potential of green chemistry remains untapped. A comprehensive chemicals policy should include information-based strategies, direct regulation, extended producer responsibility, technical assistance, market-based incentives and public support for research and education. These strategies can position California to become a national and global leader in green chemistry innovation.

"Over the next 5 to 10 years, green chemical innovation could be a significant source of competitive advantage for companies manufacturing chemicals used in consumer products."

—*European Social Investment Forum*, 2003

CLOSE THE DATA GAP:
Generate sufficient information for businesses, consumers and public agencies to choose viable alternatives

Disclosure of hazard information will enable California's businesses, consumers and policymakers to choose the alternatives that provide maximum protection of human health and the environment. This information should improve the prospects for businesses seeking to market green chemistry alternatives.

In addition to hazard information, public agencies need chemical tracking data to characterize human exposure potential. Hazard and tracking data together will help agencies identify and prioritize substances of greatest concern (see box).

Generating the data

- Chemical producers and product manufacturers should be required to provide hazard and tracking data as a condition of use or sale in California. Chemical and product distributors should also be required to contribute tracking data.
- An external independent panel should define and periodically update a set of hazard traits to provide a scientific basis for decision- making.
- California should identify the best available toxicity testing methods and support research and development of new methods.
- Toxicity testing methods and reporting of results should produce consistent data, permitting comparison of chemical hazards.
- Producers should reimburse taxpayers for the costs of California's chemical management program

Ensuring data quality

- California should provide oversight to ensure the completeness, quality and credibility of hazard and tracking data submitted by producers.
- California should adopt the highest standards for independence of experts advising the state, modeled on International Agency for Research on Cancer standards.[2]
- Hazard data must not be considered confidential business information.

Collecting and disseminating the data

- California should establish a standardized format for submission of hazard and tracking data and make that information publicly accessible online.
- To improve understanding of the links between exposures and disease, hazard and tracking data should be integrated with key California programs, including the biomonitoring program, the Environmental Health Tracking program, the Environmental Protection Indicators for California project, occupational disease surveillance programs, and the state's disease registries.[3]

DATA NEEDS[4]

Hazard:
Characterize the potential that a chemical is:
- Bioaccumulative or persistent in the environment
- Genotoxic, carcinogenic or teratogenic
- Toxic to adult or developing reproductive, neurological, endocrine or immune systems
- A respiratory sensitizer
- Acutely or chronically toxic to the heart, liver, kidney, bone marrow, eye or skin
- Toxic to aquatic organisms

Tracking:
Establish a roadmap of chemicals produced or sold in California based on a life cycle approach including:
- Sales volume and distribution
- Industrial and consumer uses
- Environmental releases
- Disposal practices

California has the resources to retool the chemical production system into one that continually develops cleaner technologies and protects its greatest assets: healthy people, vital ecosystems and a thriving economy.

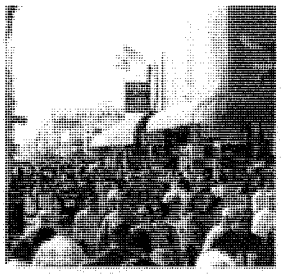
CLOSE THE SAFETY GAP: Address known hazards

To close the safety gap, California agencies need new tools to efficiently identify, prioritize, and mitigate chemical hazards. This requires a new legal framework for agencies to act on reasonable grounds for concern, even where complete hazard or tracking data is not yet available.

Prioritizing substances

- The state should create a tiered catalog of chemicals that categorizes substances according to their relative hazards. Priority should be placed on chemicals of greatest concern to the most vulnerable populations, including pregnant women, young children and workers.
- Lists developed by Canada and the European Union can provide a starting point; however, California's catalog should be tailored to reflect chemical uses specific to the state.[5]
- The cataloging system should be responsive to the introduction of new substances, changes in chemical production or sales volume, the emergence of new health effects data, and advances in hazard characterization.

California should invest in education and technical training to prepare a workforce capable of designing and producing the sustainable materials, manufacturing processes and products that are anticipated to play a key role in emerging global markets.



California can provide technical assistance to small businesses, helping them make the transition from concept to commercial application of cleaner technologies that incorporate the principles of green chemistry.

BUILDING CALIFORNIA'S GREEN ECONOMY

California's energy efficiency policies have attracted over 100 clean energy technology companies to the state.[6] Investments in the state's clean energy industry are anticipated to seed 52,000 to 114,000 new jobs statewide by 2010.[7]

By supporting economic development in the clean energy sector, California stands to gain in several ways:

- Creating new opportunities for investment in 21st-century technologies
- Providing new employment opportunities, including in California's low-income urban areas
- Reducing energy costs for residents and businesses
- Reducing the state's environmental footprint

A new chemicals policy that supports green chemistry could produce similar benefits, opening new business and employment opportunities in safer chemicals and products while also improving human health and environmental protection.

- The chemical cataloging process should not delay expedient action when a chemical's hazard potential is known or a viable safer alternative is available.

Mitigating known hazards, adopting safer alternatives

- The introduction and continued use of chemicals of particular concern should be subject to agency review and approval. Where no safer viable alternative exists, the distribution and use of such chemicals should be subject to appropriate controls. If a viable safer alternative exists, its adoption should be mandated and the chemical of concern should be phased out.
- California should require companies to periodically evaluate the availability of inherently safer chemicals and processes and report on their evaluations.
- The producer should assume the burden of establishing that a chemical is not of particular concern, or that no viable alternative is available.

Improving producer responsibility

Producers should take responsibility for the full lifecycle costs of their chemicals and products, including production, use, releases, and disposal or re-use.

- The California Integrated Waste Management Board's "Framework for Extended Producer Responsibility" should be implemented.[8]

CLOSE THE TECHNOLOGY GAP:

Support green chemistry research, education and implementation

Correcting the data and safety gaps will realign the market to support investment in green chemistry products and technologies. In addition, California can close the technology gap by supporting green chemistry research, education and implementation.

Public Support for Research

Publicly funded basic science research has underpinned California's biotechnology, pharmaceutical, and electronics industries. There is no equivalent support for green chemistry. Publicly funded research should:

- Identify the chemical information needed by businesses, agencies and consumers to make informed decisions, and how this information could be most effectively communicated.
- Develop tools for accurately and expediently evaluating the health and environmental effects of chemicals, products and mixtures, including the use of high-throughput testing and predictive toxicology methods.[9]
- Develop assessment tools for identifying safer alternatives.
- Develop methods for evaluating exposures to chemical mixtures and the cumulative effects of chronic, simultaneous exposure to multiple environmental contaminants.

Education and training
Education in green chemistry and sustainability can ensure a skilled workforce. It should be integrated across academic disciplines and included in the curriculum from elementary through graduate-level education.

California's colleges and universities should develop professional and vocational training programs in sustainability, including green chemistry.

Technical Assistance and Incentives
California's public agencies and universities should collaborate to assist companies as they:

- Transition from concept to commercial applications of sustainable practices
- Identify the risks and expenses associated with new green chemistry technologies
- Move green chemistry technologies from the laboratory to full-scale production
- Transition green chemistry technologies from niche markets to broad-scale commercial success.

California can support adoption of green chemistry technologies by:

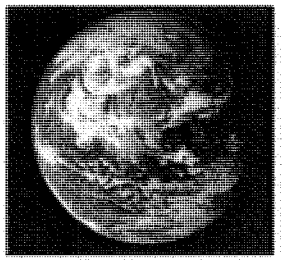
- Conducting demonstration projects of best business practices
- Developing assessment tools for identifying suitable alternatives to chemicals of concern
- Developing design standards and technical specifications
- Assessing regulatory obstacles to innovation of safer chemicals and processes.

Identify safer alternatives

- California should develop technical criteria to define the attributes that qualify a chemical or process as a safer alternative.
- These criteria should prevent shifting of hazards from one population or environmental medium to another.
- California should consider establishing a list of viable safer alternatives as a basis for phasing out hazardous products and processes.

Market-based incentives
Targeted market-based incentives can also accelerate the adoption of green chemistry. These include:

- A state procurement system for preferred chemicals and products
- Green chemistry certification and labeling standards
- Low-interest loans for investment in green chemistry technologies
- Tax credits for meeting hazard reduction targets and for improvements in health and environmental performance that exceed standard industry practice



California's ability to link economic opportunity with human health and environmental protection will be a cornerstone for a sustainable future.

- Recognition awards for leading industries.

CALIFORNIA IS POISED TO MEET THE CHALLENGE

A modern, comprehensive chemicals policy will address California's pressing health, environmental and economic problems associated with the management of chemicals and products. Such a policy will promote the science, technology, and commercial applications of green chemistry: the design, production and use of chemicals, processes and products that are safer for humans and the environment.

Building new productive capacity in green chemistry will support a vibrant economy, open new opportunities for investment and employment, and protect human health and the state's natural resources. Given California's unparalleled innovative potential and its scientific, technical and financial resources, the state is well-positioned to become a national leader in green chemistry innovation.

Senator BOXER. Thank you so much for your moving testimony.

Mr. DeLisi, Fanwood Chemical, Inc., Synthetic Organic Chemical Manufacturers Association, minority witness, welcome, sir.

STATEMENT OF V.M. DeLISI, PRESIDENT, FANWOOD CHEMICAL, INC.

Mr. DELISI. Good morning, Chairman Boxer and distinguished members of the Committee. My name is Jim DeLisi, I am President of Fanwood Chemical, located in Fanwood, New Jersey, and I might add, the proud father of two grown daughters and a grandfather of one.

I have been employed by Fanwood Chemical for over 30 years, and have specialized in the marketing of organic chemical intermediates in North America as well as Europe and South America. In addition, I have been heavily involved in trade issues that impact our industry. I have served as chairman of the Synthetic Organic Chemical Manufacturers Association, better known as SOCMA's International Affairs Committee for many years. In addition, I am the Chairman of ITAC 3, the Industry Trade Advisory Committee for Chemicals, Pharmaceuticals, Health Science Products and Services administered jointly by the United States Department of Commerce and the United States Office of the Trade Representative.

Thank you for this opportunity to share with you my company's perspective on current chemical risk management regulations and initiatives by the U.S. Environmental Protection Agency. My remarks will also address generally significant concerns about Congress moving in the direction of adopting over-reaching regulatory schemes, such as Europe's Registration, Evaluation, Authority and Restrictions of Chemicals Program, better known as REACH.

Fanwood Chemical currently has two full-time employees and two part-time employees working from our offices in Fanwood, New Jersey. We also have a working relationship with senior members of our industry for help on special projects. The products we sell are primarily used to make color or are functional additives in lubricating fluids. In these instances, we are responsible for bringing to the marketplace products produced in U.S. manufacturing facilities and are backed up by their staffs.

We are also experts in REACH and the business challenges this program presents, with special emphasis on its impact on non-EU based companies. This combination of activities has required us to have a working knowledge of EPA's Toxic Substances Control Act, the Federal Insecticide, Fungicide, Rodenticide Act and many other EPA programs, as well as similar programs in countries where we have direct exports. We also are knowledgeable in programs for countries where have indirect exports, i.e., our customers export our products to those lands.

Fanwood Chemical was founded by my father, Vince DeLisi, in 1971. He could have very successfully completed his career in the chemical industry without at all ever leaving the shores of the United States. However, the primary industry we were serving at the time was the manufacturers of dyestuffs, so I clearly could not have had a successful career only within the bounds of the United States. Therefore, in 1980, we began to do business in the inter-

national arena, first into Europe. It was a challenge then and continues to be a challenge today to sell U.S.-produced goods internationally because of severe competition we face from all over the world.

Since 1976, thousands of chemicals have been evaluated by the U.S. Environmental Protection Agency under the Toxic Substances Control Act for potential human health and environmental effects. American chemistry has invested and continues to invest significant resources to assure that products we sell meet rigorous regulatory standards and do not present an unreasonable risk to the health of the environment. To the contrary, in fact, chemicals produced by SOCMA members daily improve the lives of millions of Americans. These chemicals assist the young and the elderly alike, helping the healthy to stay well and the sick to recover. Other chemicals produced by industry go toward defending our Nation against terrorism, enabling American workers to perform their jobs safely and transporting millions of travelers across our Nation. We are also confident that chemistry will likely be the key to solutions to minimize global warming. All of these benefits are made possible by the appropriate balance in our existing system of chemical control regulation and the vast commitments of chemical industry resources to product stewardship.

I urge this Committee to thoughtfully consider whether it is really necessary or wise to adopt a monolithic new regulatory regime for chemical regime like the EU's REACH, Registration, Evaluation, Authorization and Restriction of Chemicals, program. In our view, existing EPA regulation and voluntary initiatives are sufficient and far more appropriate than REACH, to control possible hazards and still preserve the sustainability of America's third largest manufacturing industry.

Our industry accepts our responsibility to profitably make products that are safe under expected exposure conditions, an obligation that EPA polices under TSCA. But Congress has also established a policy in TSCA that chemical regulations should not impede unduly or create unnecessary economic barriers to technological innovation. This balance of regulatory burdens and public benefit is crucial for small American business which would be hit hardest by a REACH-type scheme.

A common assumption that chemical companies each employ thousands of workers and have unlimited resources are myths. Seventy percent of SOCMA members, many of which operate in New Jersey, are classified as small business by the Federal Government. Though not a manufacturer in the pure definition, Fanwood Chemicals sells chemicals domestically and abroad to manufacturers that produce end-use products. Manufacturers large and small rely on companies like mine to source chemicals on their behalf, enabling them to reliably meet American consumers' demand for their products. In a major way, Fanwood Chemical and the many small companies like it represent the underpinnings of the industry. Although we are small, our regulatory obligations are very similar——

Senator BOXER. Sir, I want you to conclude.

Mr. DELISI. OK.

Senator BOXER. Yes.

Mr. DELISI. We believe that an American REACH would not only hamper innovation but reverse the progress made over the course of many years by Federal regulators in the chemical industry. Thank you for this opportunity to share with you Fanwood Chemicals' perspectives on these issues.

[The prepared statement of Mr. DeLisi follows:]

Oral Statement of

V.M. DeLisi
President
Fanwood Chemical, Inc.

before the

United States Senate
Committee on Environment and Public Works

On

Oversight on U.S. Chemical Risk Management Policy

April 29, 2008

Good morning Chairman Boxer, Ranking Member Inhofe, and Distinguished Members of the Committee. My name is Jim DeLisi, President of Fanwood Chemical, Inc., located in Fanwood, New Jersey. I have been employed by Fanwood Chemical for over 30 years and have specialized in the marketing of organic chemical intermediates in North America as well as Europe and South America. In addition, I have been heavily involved in trade issues that impact our industry. I have served as Chairman of the Synthetic Organic Chemical Manufacturers Association's (SOCMA) International Affairs Committee for many years. In addition, I am the Chairman of ITAC 3, the Industry Trade Advisory Committee for Chemicals, Pharmaceuticals, Health Science Products and Services administered by the US Department of Commerce and the Office of the United States Trade Representative.

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Fanwood Chemical was founded by my father, Vince DeLisi in 1971. He could have successfully completed his career without being involved in the international arena. However, the primary industry we were serving at the time was manufacturers of dyestuffs, so clearly I could not. Therefore in 1980 we began to do business in the international arena – first into Europe. It was challenging then, and remains challenging today to sell U.S.-produced goods into the Colorant Industry internationally because of the competition from the Far East.

Since 1976, tens of thousands of chemicals have been evaluated by the U.S. Environmental Protection Agency under the Toxic Substances Control Act for potential human health and environmental effects. American chemistry has invested and continues invest significant resources to assure that the products we sell meet rigorous regulatory standards and do not present an unreasonable risk to health or the environment. To the contrary, in fact, chemicals produced by SOCMA members daily improve the lives of millions of Americans. These chemicals assist the young and the elderly alike, helping the healthy to stay well and the sick to recover. Other chemicals produced by industry go toward defending our nation against

terrorism, enabling American workers to perform their jobs safely, and transporting millions of travelers across our Nation. We also are confident that chemistry will be key to the solutions needed to help us minimize global warming. All these benefits are made possible by the appropriate balance contained in our existing system of chemical control regulation and the vast commitment of chemical industry resources to product stewardship.

I urge this committee to thoughtfully consider whether it is really necessary or wise to adopt a monolithic new regulatory regime for chemical regulation like the European Union's Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) regulation. In our view, existing EPA regulations and voluntary initiatives are sufficient, and far more appropriate than REACH, to control possible hazards and still preserve the sustainability of America's third largest manufacturing industry. Our industry accepts our responsibility to profitably make products that are safe under expected exposure conditions – an obligation that EPA polices under TSCA. But Congress has also established a policy in TSCA that chemical regulation should not "impede unduly or create unnecessary economic barriers to technological innovation." This balance of regulatory burdens and public benefit is crucial for small American businesses, which would be hit hardest by a REACH-type scheme. A common assumption that chemical companies each employ thousands of workers and have unlimited resources are myths. Seventy percent of SOCMA members, many of which operate in New Jersey, are classified as small businesses by the federal government. Though not a manufacturer in the pure definition, Fanwood Chemical sells chemicals domestically and abroad to manufacturers that produce end-use products. Manufacturers large and small rely on companies like mine to source chemicals on their behalf, enabling them to reliably meet American consumers' demands for their products. In

a major way, Fanwood Chemical and the many small chemical companies like it represent the underpinnings of the industry. And, though we are small, our regulatory obligations are very similar to large manufacturers covered by TSCA, which we accept, but are deeply concerned with Congressional rhetoric that suggests that the EU's REACH program is somehow a better program with negligible impact on U.S. industry.

We believe that an "American REACH" would not only hamper innovation but would reverse the progress made over the course of many years by federal regulators and the chemical industry to appropriately manage risk. Even before the first REACH compliance deadline has passed, we are already witnessing how bogged down the process of regulating chemicals has become in Europe. Whether REACH will improve human health or the environment will not be known for years, if ever, but its ability to tie up regulators and commerce is already clear. In short, REACH has outreached the EU's capabilities. Americans cannot afford to emulate this unproven, highly bureaucratic approach to chemical regulation, especially when we already possess a system that has proven its mettle and needs only revitalization.

Thank you for the opportunity to share with you Fanwood Chemical's perspective on chemical control regulations in the U.S. I look forward to your questions.

Senator BOXER. Thank you very much.

Next is Dr. Laura Plunkett, Ph.D., Integrative Biostrategies, LLC, a minority witness. Welcome.

STATEMENT OF LAURA M. PLUNKETT, PH.D., DABT, INTEGRATIVE BIOSTRATEGIES, LLC

Dr. PLUNKETT. Good morning, Madam Chairman and Senators. I want to thank you for the opportunity to be here today to speak to you.

My name is Dr. Laura Plunkett. I am a pharmacologist, toxicologist and a human health risk assessor. In my job every day I look at these issues related to what chemicals in our environment are affecting our health. I work for industry sometimes, but I also work for individuals, and often give advice to individuals or work on cases where individuals have been harmed by chemicals or by individual consumer products. So I can look at this from both perspectives.

My testimony today is related to the adequacy of current risk assessment methods and regulatory programs to evaluate chemicals and identify risks to sensitive populations in the human population. That includes the developing fetus, infants and children. I would like to say that this testimony reflects my views, not the views of my clients.

The first thing I want to do is briefly define risk assessment, even though a former witness did that for us. Risk assessment is a process, a multi-step process within the regulatory environment. Risk is defined as the probability that any injury, disease or health effect, even something as terrible as death, will occur from contact or exposure to a chemical. I am going to limit my comments to chemical risk assessment today.

It is a four-step process involving hazard identification, dose response assessment, exposure assessment and risk characterization. Each part of the process is very important in being able to determine whether or not something we are exposed to is truly going to harm us.

There is a large body of published, peer-reviewed scientific literature available that speaks to the adequacy of our current risk assessment process that is used by EPA to protect human health. The large body of studies and information out there speaks specifically to the health and the protection of the health of sensitive human sub-populations, such as the fetus, infants and children. I have reviewed and analyzed this large body of information over the years I have worked as a consultant, and I would like to speak just very briefly to a few of the key points or principles that I think you can glean as a scientist looking at this literature.

The first point, as I think everyone is aware, children are not little adults. Age and stage of development are extremely important to risk assessors. We use those things as considerations in our process. Children, while not being little adults, their sensitivity to chemical exposure is highly dependent on the nature of the chemical. There are chemicals where children are more sensitive and are the population of concern for the risk assessment. There are chemicals where in some cases it is a different population, the elderly, for example, that may be of most concern. In some cases, children

can actually be less sensitive than the mature human adult to the exposure to the chemical.

Age is not the only factor that contributes to differences among humans in the response to chemical exposures. Gender, genetics and health status are also very important, and in some cases, more important than the age. Exposure, however, is one of the most critical components in the process. We know that there are a lot of data showing that children can be exposed to a greater extent to chemicals in their environment, due to things that they do daily in their environment. All of those things are currently employed and used as part of the risk assessment process. We do children-focused or child-focused parts of our assessment when a child is the receptor or the individual that is of concern to the risk assessment.

If you do an analysis and look at the studies overall, and try to do what I call a weight of the evidence approach to examining the published literature, you can see that the methods that EPA currently uses for its risk assessment indeed give a risk assessor some confidence that the developing fetus, infants and children are being protected. Remember that the methods we are looking at include consideration of differential sensitivity, not only to toxicity, but also on the exposure side.

Current risk assessment methods for chemicals employ tiered-testing strategies as a common thing that we see today. That is what the current regulations use. They allow the risk assessor to look at the fact that resources are being focused on evaluation of the chemicals of most concern and also looking at the population of most concern. They allow you to prioritize the chemicals for further testing. That is an important part of the process.

So when I look at this data and also the regulations that are currently in place, as a scientist, I believe that we can have some confidence that we are protecting the fetus, infants and children with the approaches that are currently in place.

This fact, combined with the fact that we know that hazard is not the only part of the equation, but also we need to know something about the exposure and the overall risk of the chemical that we look at, that is an important part of the equation is well.

Enforcing a chemical regulation is also a focus. I think that is part of the process. When you look at TSCA, if enforcement is done as can be done, indeed I think that the chemical regulatory process can be complete and protective of human health for all sub-populations.

I have a few seconds and I just wanted to make a couple of comments to some of the things that I have heard before.

Senator BOXER. Actually, you have gone over. You have gone 31 seconds over, but if you want you can go another 30 seconds. Go right ahead.

Dr. PLUNKETT. I just wanted to say that in some of the comments that I have heard, and some of the studies and some of the statistics that have been brought up by the other witnesses, as a scientist, I am not aware that some of those statistics are indeed true. I would encourage people on the panel to use——

Senator BOXER. What statistics?

Dr. PLUNKETT. Some of the statistics about the rate of cancer incidence increasing, the level that it has increased over the years.

I think if you look at the literature, those numbers, at least the numbers that I am aware of are not supported by the scientific literature, at least. I will end it there.

[The prepared statement of Dr. Plunkett follows:]

Discussion of the Adequacy of Current Regulatory Risk Assessment Approaches for Protection of Children's Health and the Health of Other "Sensitive" Human Subpopulations

Testimony of

Laura M. Plunkett, Ph.D, DABT
Integrative Biostrategies, LLC
Houston, Texas

April 29, 2008

Before the
Senate Environment and Public Works Committee

Laura M. Plunkett, Ph.D., DABT
April 29, 2008

My name is Dr. Laura Plunkett. The following is my testimony regarding the adequacy of current risk assessment methods used by EPA to evaluate chemicals for identifying risks to sensitive human subpopulations such as the developing fetus, infants and children. This testimony reflects my own views as a pharmacologist, toxicologist and risk assessor. The views presented are my independent perspectives as a scientist and are not the views of my clients.

A. Qualifications

1. I am a pharmacologist, toxicologist, human health risk assessor, registered patent agent, and principal of a consulting company known as Integrative Biostrategies, LLC. Integrative Biostrategies is a consulting firm that works at the interface of the biological sciences, regulatory affairs, and business decisions to provide its clients with science-based solutions to issues associated with product development and stewardship. Prior to becoming a partner in Integrative Biostrategies, I was head of Plunkett & Associates, a health and environmental sciences consulting firm based in Houston, Texas. I have over twenty years of experience in the areas of pharmacology and toxicology and have worked in both government and academic research and have taught pharmacology and toxicology at the undergraduate and postgraduate levels. I am board-certified as a Diplomate of the American Board of Toxicology. I am a member of several professional organizations, and have authored or co-authored numerous scientific publications.

2. I received my B.S. degree in 1980 from the University of Georgia, and a Ph.D. in pharmacology from the University of Georgia, College of Pharmacy, in 1984. My doctoral research was focused in the area of cardiovascular pharmacology and

specifically dealt with delineating mechanisms responsible for the cardiac toxicity of digitalis glycosides. My doctoral training, however, covered all aspects of pharmacology and toxicology, including reproductive and developmental effects of drugs and chemicals. From June of 1984 through August of 1986, I was a Pharmacology Research Associate Training (PRAT) fellow at the National Institute of General Medical Sciences, Bethesda, Maryland. I worked in a neurosciences laboratory of the National Institute of Mental Health. From September 1986 to June 1989 I was an Assistant Professor of Pharmacology and Toxicology in the medical school at the University of Arkansas for Medical Sciences, Little Rock, Arkansas where I performed basic research in the areas of neuropharmacology and toxicology as well as cardiovascular pharmacology and toxicology. I taught courses for both medical students and graduate students in pharmacology and toxicology as well as the neurosciences.

3. From December of 1989 to August 1997 I worked for ENVIRON Corporation, first in the Arlington, Virginia office and then in the Houston, Texas office. At ENVIRON, I worked specifically within the health sciences group and most of my projects dealt with issues surrounding the effects of chemicals on human health. During my consulting career at ENVIRON, while with Plunkett & Associates, and now at Integrative Biostrategies, I have worked on a variety of projects dealing with the regulation of products by the U.S. Environmental Protection Agency (EPA) including pesticides and industrial chemicals, as well as working on projects dealing with assessing risks to human health due to exposure to chemicals through the environment (*i.e.*, air, water, soil, food). Many of the projects I worked on while at ENVIRON, while at Plunkett & Associates, and now at Integrative Biostrategies have involved evaluation of

the reproductive and developmental effects of drugs and environmental chemicals, with a focus on the protection of children's health. A true and correct copy of my current curriculum vitae is attached hereto as Appendix A.

B. Introduction

4. I have been asked to provide a risk assessor's perspective on issues related to the adequacy of current regulatory risk assessment approaches for protection of children's health. I have worked in the area of risk assessment and children's health for over 15 years, with some of my first work related to preparation of a chapter for the proceedings of a 1990 conference organized by the International Life Sciences Institute (ILSI) entitled *Similarities and Differences Between Children and Adults: Implications for Risk Assessment* (held November 5-7, 1990, Hunt Valley, MD). The chapter I authored discussed issues related to exposure differences between children and adults (Plunkett, et al. 1992). Since that time, I have worked actively to study and analyze data defining the biological basis for age-related differences in chemical toxicity as well as the methods used to assess risks to humans at all stages of development (from development *in utero*, infancy, childhood, adulthood and with aging).

5. Review of the extensive published literature relating to human sensitivity due to age and stage of development and the methods used to assess risks due to chemical exposures reveals several key principles and findings including:

- Children are not "little" adults. Age and stage of development are important factors in assessing risks due to chemical exposures.

- Although children are not "little" adults, their sensitivity to chemical exposure is highly dependent on the nature of the chemical. In some cases children are more sensitive, in some cases there is no difference in sensitivity, and in some cases they are less sensitive.
- Age is not the only factor related to human variability in chemical toxicity responses. Other factors include gender, genetics, and health status. In some cases, age is less important than other human factors such as genetics.
- Apart from differences in sensitivity to toxic responses, exposure is a critical consideration when age is of concern. In fact, available data indicate that exposure differences between infants, children and adults is often more important when assessing risks in order to ensure that all human populations are protected.
- It is a general consensus of scientists in the published literature that the use of uncertainty factors[1] allows risk assessors to develop health risk values that are protective of all potentially sensitive human populations, including children.
- Analysis of studies in the published, peer-reviewed literature reveals that currently available risk assessment methods, methods used by EPA, have provisions in place that allow the risk assessor to ensure that the developing fetus, infants and children are protected. These provisions include accounting for differential sensitivity in toxic responses as well as differences in exposure.
- Finally, current risk assessment methods for chemicals that employ tiered-testing strategies allow resources to be focused on the evaluation of the most sensitive adverse effects of chemical exposures of greatest concern but are also adequate to

[1] The term "uncertainty factor" is defined and discussed in detail later in section D.

assess potential risks to sensitive human populations such as the developing fetus, infants, and children.

6. Based on consideration of all of the available data relevant to assessing the adequacy of current risk assessment methods to protect human health, I believe that there are sound, scientific data that demonstrate the adequacy of current risk assessment methods to protect human health, including sensitive subpopulations such as children. This fact, combined with the knowledge that hazard alone is not sufficient to characterize actual risk, would argue against a need to develop alternative regulatory approaches for chemicals when the concern is protecting children's health.

C. Overview of the Risk Assessment Process

7. "Risk assessment" is a tool used by scientists and regulators to help decide what restrictions to place on the uses of chemicals and to determine the risks to humans posed by exposure to chemicals in the environment. "Risk" is defined as the probability that injury, disease or death may result from a chemical exposure under certain specific circumstances. All human activities are associated with some degree of risk to health and well-being, activities such as driving a car, climbing a ladder, crossing a street, or even taking a bath or shower. In the context of chemical risk assessment, the term "safe" does not mean without risk. Instead, a "safe" level of chemical exposure is a level with which there is "practical certainty" that no harm will result in exposed individuals.

8. In 1983, the National Academy of Sciences outlined the steps that should be included in any scientifically sound risk assessment process (NAS 1983). They

defined risk assessment as the characterization of the probability of potentially adverse health effects from human exposures to environmental hazards (*e.g.,* chemicals). The NAS included four basic steps in every complete risk assessment: hazard identification; dose-response assessment; exposure assessment; and risk characterization. Each of these four steps is critical to assuring that scientifically sound decisions can be made by regulators when those decisions are being made about the impact of chemical exposures on human health.

Step 1: Hazard identification This step involves gathering and evaluating toxicity data on the effects of chemical on body systems and the exposure conditions necessary to produce those effects. Risk is not assessed at this stage but instead the scientist or regulator focuses on whether the effects seen in toxicity studies are relevant and useful for assessing risk, and which effects should be the focus of the risk assessment. It is important to note that in the case of most chemicals, hazard information will be in the form of laboratory animal toxicity studies, not studies in humans. Although laboratory animals are not "small humans", it is a general principle of both pharmacology and toxicology that the types of effects (qualitative) seen with chemical exposure in mammalian species are predictive of the types of effects to be expected in humans. This general principle has been validated over a century of chemical testing in animals.

Step 2: Dose-response assessment Dose-response assessment is a critical step and a critical concept. It involves quantifying the relationship between exposure to a chemical and the extent of injury or disease produced. It is a basic principle of toxicology that "the dose makes the poison", or in other words

that all chemicals can produce adverse effects at some dose. This is a guiding principle for development of human drugs where physicians need to know at what dose the drug/chemical produces beneficial effects as well as the dose of the drug/chemical that is associated with adverse effects. It is important to note that the dose that produces a particular effect in an animal will not always be the dose that will have that same effect in humans. Animals are assumed to be less sensitive to the effects of chemical exposures than humans and as a result, studies performed in animals are routinely performed at doses that greatly exceed any anticipated or measured level of human exposure.

Step 3: Exposure assessment This step is an important consideration in the risk assessment process and involves describing the nature and size of various populations exposed to a chemical as well as the magnitude and duration of exposure. Many human health risk assessments look at past, present, as well as future or expected exposures. It is another general principle of toxicology that exposure is a necessary action for toxicity to occur. In other words, unless a human is exposed to the chemical, the chemical does not pose a risk to health. EPA currently has in place methods for considering infants and children as separate exposed populations apart from adults, allowing a risk assessment to consider and account for differences in exposure patterns.

Step 4: Risk characterization This is the final step in the risk assessment process where the results of the first three steps are integrated and analyzed. In this step the likelihood that the human population of interest would experience any toxic effects from chemical exposure is determined.

9. Because it is highly unlikely that the scientist or regulator will have complete information on any chemical for each of the first three steps in the risk assessment process (hazard identification, dose-response assessment, exposure assessment), regulatory risk assessments have developed a process for quantifying "uncertainty" in the assessment, where "uncertainty" is a measure of the level of confidence the risk assessor has in the data that is used. "Uncertainty" is also a measure of the level of variability that is always seen within a population, in terms of variability in response as well as variability in exposure. The most common approach to quantifying uncertainty has been to apply "safety factors" or "uncertainty factors" during the risk assessment. The use of such uncertainty or safety factors is an important concept in the discussion of protection of children's health.

D. What Are Safety Factors or Uncertainty Factors?

10. "Safety factors" were first introduced in the 1950's by scientists at the U.S. Food and Drug Administration (FDA) as part of the process for assuring the safety of humans exposed to food additives and food residues of pesticides. These factors were used to account for the variability in biological responses between animals and humans (interspecies variability) and between individuals in the human population (intraspecies variability). These scientists had recognized that variability in biological responses between animals and humans was generally within a range of two to three-fold while the variability among individuals of both sexes, all ages, and of different states of health generally fell within a range of a factor of 10. As a result, when the FDA was determining what a safe level of exposure to a food additive might be for humans in the

general population, they applied a factor of 100 to the level they determined in an animal study to be without any adverse effect on health. This 100-fold factor was applied to the endpoint in an animal study that was the most sensitive endpoint (lowest effect dose) from the most sensitive species.

11. In the context of risk assessments at the EPA, the agency which is responsible for assessing risks to humans posed by chemicals in the environment (air, water, and soil), and often termed unintentional exposures[2], agency scientists have employed a similar approach to assessing risk by using "uncertainty factors". "Uncertainty factors" are again those factors used to account for variability in biological response and population exposure. However, the factors have a more complex application and are defined even more specifically in terms of the exact type of variability that is being measured and corrected for during the risk assessment.

12. There are currently at least six different uncertainty factors (UFs) that are employed as part of a chemical risk assessment: interspecies UF; intraspecies UF; subchronic to chronic UF; LOAEL to NOAEL UF[3]; incomplete data base UF; and modifying UF. Each of these UFs is typically a factor of 10, although the value of any one UF can be reduced from 10 to either 3 or 1 when available data support such a reduction. These factors are used by risk assessors to ensure that the risk values quantified are protective of human health, including the health of sensitive human subpopulations. The interspecies and intraspecies UFs are routinely applied in chemical

[2] In the context of this discussion, an unintentional exposure is an exposure that occurs due to breathing air, drinking water, contacting soil or other types of particulate matter on surfaces, and eating food (exceptions would be intentional food additives).

[3] LOAEL is an acronym for the "lowest observed adverse effect level", which is typically the lowest dose in an animal study at which some type of adverse effect is seen. NOAEL is an acronym for the "no-observed adverse effect level", which is typically the dose in an animal study at which no adverse or toxic effects are seen. Another acronym related to NOAEL is NOEL or "no observed effect level" , which is the dose in an animal study at which absolutely no effect of any kind (adverse of not) is observed.

risk assessment and are considered part of standard risk assessment practice. The other four UFs are applied only when appropriate, mainly in cases where the quality or quantity of the available toxicology data is lacking. The typical UFs used in chemical risk assessment can be described as follows:

Intraspecies UF Used in most chemical risk assessments to account for variation in sensitivity to toxic responses among humans. The major characteristics that are believed to contribute to variation in sensitivity include gender, age, genetics, and disease state. Note that age in this case would include the differences between adults and developing fetuses, infants and/or children. Studies have indicated that an intraspecies UF = 10 is more than adequate to assure protection of all sensitive human subpopulations (to be discussed in more detail below in section E).

Interspecies UF Used in most chemical risk assessments to account for variation in sensitivity to toxic responses between animals and humans. Studies have indicated that an interspecies UF = 10 is adequate to account for differences between species in almost all cases examined.

Subchronic to Chronic UF This UF is applied when the animal studies to be used in the risk assessment involved shorter durations of exposure than the expected human exposure. For example, if the animal study to be used involved only dosing for one month but humans could be exposed throughout their lifetime, than an additional UF = 10 would be applied to account for the potential effect of duration of exposure on level of response.

LOAEL to NOAEL UF This UF is applied when the animal study to be used in the risk assessment did not identify a NOAEL, or a level where there were no adverse effects following chemical exposure. Instead, the study identified a LOAEL. In this case, an additional UF = 10 would be applied.

Incomplete data base UF This is an important UF for many chemical risk assessments and allows the risk assessor to account for a lack of certain types of studies on any one chemical. For example, in the case of concern for children's health, if the toxicity study data base for a chemical lacked testing in pregnant animals or in developing animals, then an additional UF = 10 might be applied in the risk assessment. In this way, the use of the additional UF allows the risk assessor to account for the inability of any single study to adequately address all possible adverse outcomes.

Modifying Factor Although this factor is not routinely applied in risk assessments, it is another way that the risk assessor can correct for perceived deficiencies in the studies being used. For example, if an animal study was deficient in some design characteristic such as the number of animals being tested or lack of testing in both sexes, then a modifying factor from some value > 1 to 10 could be applied in the risk assessment.

13. Published literature and regulatory guidance documents have weighed in on the appropriate uses and magnitude of UFs for datasets with a variety of deficiencies or limitations, as well as for datasets that are believed to lack certain types of toxicity studies (*e.g.*, Dourson et al. 1996; Dourson et al. 2002; see also various risk assessment

guidance documents available on the EPA and FDA websites). As discussed in some of these references, composite UFs of 100 are routinely applied (interspecies and intraspecies UFs) but that composite UFs of as high as 3,000 or 10,000 are also possible depending on the quantity of quality of the data used in the risk assessment. Most risk assessors believe, however, that if a composite UF of greater than 10,000 is deemed necessary, then a quantitative risk assessment should not be performed until more reliable and relevant data are available. In the case of EPA, the agency would seek submission of additional data by companies. It is a general consensus of scientists in the published literature that the use of UFs allows risk assessors to develop health risk values that are protective of all potentially sensitive human populations, including the developing fetus, infants, and children.

E. Do Currently Available Risk Assessment Methods Protect the Developing Fetus, Infants, and Children?

14. As discussed in the introduction to this testimony, the critical question to be addressed is whether current risk assessment methods are adequate to ensure protection of human health for individuals of all ages, including the developing fetus. In order to best answer this question, I reviewed the published literature to identify studies that have attempted to answer this question with actual analysis of data rather than simply opinion based on common practice.

15. The focus of many of the available studies is whether the difference in sensitivity among human populations is adequately accounted for by an intraspecies UF of 10. In Table 1 below, I have listed the studies that focus on comparisons of adults with

either children or infants. There is also a body of studies that focus on adults and the variation due not to age but instead other factors such as genetics, sex and disease state (*e.g.*, Dourson and Stara 1983; Brown 2001; Hattis et al. 1999a, 1999b; Brock 1991; Hattis 1987; Calabrese 1985; Renwick and Lazarus 1998; Renwick et al. 2001; Silverman et al. 1999; Nong and Krishnan 2007). Regardless of the comparison group examined (studies focusing on age; studies focusing on issues other than age), the results were the same. The data consistently showed that the level of variability in response among the human population is adequately accounted for by a UF of 10 for intraspecies variability, or by a UF of 3.16 if only the toxicokinetic component of the intraspecies UF is being considered[4].

Table 1

Studies Reporting Analysis of Data on Age-Related Variability Within the Human Population that Could Affect Chemical Risk Assessment

Citation	Study Type	Conclusions
Glaubiger et al. 1982	Compared human MTDs[1] of oncology drugs in children vs. adults	No significant difference in toxicity seen between adults and children, indicating an intraspecies UF of 10 is conservative for this class of highly toxic chemicals, where chemicals are given at high doses.
Sheehan and Gaylor 1990	Compared animal LD50[2] ratios of adults vs. young animals.	Among 238 chemicals tested, 86% of the time the UF = 10 would be sufficient to account for variability.
Rane 1992	Compared human newborn vs. adult clearance values	For the majority of the chemicals considered (67%)

[4] In recent years, it has been suggested that the intraspecies UF be split into 2 components (3.16 and 3.16). One component is said to account for variability in pharmacokinetics and the other for variability in pharmacodynamics. Therefore, some of the studies in Table 1 looked at the adequacy of a factor of 3.16 not 10.

	for chemicals (toxicokinetics only considered).	a UF of less than 3.16 would be sufficient to account for variability.
Renwick 1998	Compared clearance and elimination of a variety of drugs in adults vs. infants and children (toxicokinetics only considered).	For 91% of the chemical considered a UF of less than 3.16 would be sufficient to account for variability.
Burin, G.J. and D.R. Saunders. 1999. *Regul. Toxicol. Pharmacol.* 30:209-216	A weight-of-the-evidence assessment of data available at the time that addressed the issue of human variability in risk assessment.	Reported that the use of a intraspecies UF = 10 would be protective of various human subpopulations including infants and children.
Charnley and Putzrath 2001	Comparison of animal cancer testing results across chemicals by age	Results were chemical-specific not age specific. Young animals were less susceptible than adults 47% of the time, equally sensitive 13% of the time, and more sensitive 40% of the time.
Calabrese 2001	Compared animal LD50 ratios of adults vs. young animals.	Among 313 chemicals tested, 86% of the time the UF = 10 would be sufficient to account for variability.
Naumann 2001	Compared kinetic and dynamic endpoints among humans of different ages (adults, elderly, children, and even those with diseases).	Across classes of drugs examined, authors found that the level of variability for toxicokinetics and dynamics separately would be accounted for by currently used UFs (3.3 and 3.3).
Pelekis et al. 2001	Compared pharmacokinetic parameters for volatile organic compounds in children vs. adults.	Currently used UFs for intraspecies variability are adequate without addition of an additional child-specific UF.
Skowranski and Abdel-Rahman 2001	Compared toxicokinetic factors between children, adults and the elderly.	Of the 6 drugs examined, the level of variability always fell within the a UF of 10, considering both kinetics and dynamics.
Ginsberg et al. 2002	Compared pharmacokinetic parameters for 45 different	Results show that the toxicokinetic portion of the

	chemicals (drugs) in adults versus children of various ages (included neonates).	intraspecies UF (3.16) was sufficient to account for the variability seen due to age/development.

1 MTD = maximum tolerated dose; represents a dose in animal studies that can be tolerated for the length of the study without causing either death of significant morbidity
2 LD50 = lethal dose for 50% of the population studied

16. It is clear from examination of Table 1 that the available studies support the adequacy of a 10-fold intraspecies UF to protect children's health. These data are an important part of the reason why current risk assessment approaches, that include use of UFs to determine risk, are stated to be protective of human health for individuals of all ages and stages of development.

17. Another important consideration when assessing the adequacy of current risk assessment methods to protect children's health is that when data on a chemical of concern do not include studies that have examined the potential toxicity in developing fetuses or young animals, standard risk assessment practices would dictate use of additional UFs. In those cases, an additional 10-fold UF could be employed to account for the lack of testing of the population of concern.

18. A question that is often raised in the context of protecting children's health is the question of the adequacy of current toxicology testing methods to assess risks in humans, in particular developing humans. The case study often pointed to is lead exposure. Critics of current methods suggest that without more sophisticated testing of neurological function during development, any risk assessment strategy would result in inadequate protection of children from the hazards of lead exposure. However, in an analysis I performed and published in the peer-reviewed literature in 1999, I showed that

using current methods of testing (guideline FIFRA testing) a safe exposure level in humans would have been set that is below the current regulatory action level for lead, without the use of any additional UF other than the standard intraspecies and interspecies factors (10 x 10 = 100). This is an important finding as it emphasizes that not only are current risk assessment methods protective of children's health but that toxicological testing methods that have been in use for decades are adequate to capture the level of risk posed by one of the most widely cited children's health hazards, lead exposure.

19. It is important to realize that the standard toxicological testing paradigm for industrial chemicals has been based on the use of a tiered testing framework. For example, when EPA challenged the chemical industry in 1998 to generate OECD SIDS[5]-level hazard screening data sets for HPV chemicals, under the HPV Challenge Program, companies formally committed to gather and make publicly available existing SIDS-level screening data on HPV chemicals. For each of the HPV chemicals sponsored in the program, industry provided 17 types of information, including summarized results in four categories: physical-chemical properties, environmental fate, and potential to induce toxicity in aquatic organisms and humans. Human toxicity data requested included studies assessing acute toxicity, subchronic toxicity, genotoxicity, and developmental and reproductive toxicity. The information required for human health hazard assessment in the HPV Challenge Program was identical to the internationally-agreed SIDS standards, established by the 30 nations of the OECD. The SIDS and HPV screening level test battery therefore included assessment of toxicity endpoints directly relevant to the

[5] "OECD-SIDS" is the Organization of Economic Cooperation and Development-Screening Information Dataset and refers to a chemical testing battery. The OECD created the Screening Information Data Sets program, commonly known as "SIDS," to secure uniform sets of hazard-screening information on industrial chemicals worldwide. The OECD SIDS standards comprise a series of data sets, tests, testing protocols, and information formats for conducting basic hazard assessments of industrial chemicals.

developing fetus, infants and children (*e.g.,* inclusion of reproductive and developmental toxicity testing with evaluation of sensitive life stages). Further, the standard toxicity testing battery for chemicals includes neurotoxicity assessments since all *in vivo* animal tests include observational endpoints for changes in behavior. In a recent paper (Becker et al. 2007), a tiered toxicity strategy similar to those used as part of the HPV Challenge and OECD-SIDS was proposed and evaluated. In this paper it was shown, using a retrospective validation approach, that the proposed tiered toxicity testing strategy was able to reliably identify chemicals which posed particular hazards to human health, including endpoints relevant to developing organisms. Further support for the use of tiered testing and evaluation for chemical risk assessment is found in the statements of the 2005 report of a committee of the National Academy of Sciences:

> *"Current approaches to toxicity testing include testing batteries, tiered testing, tailored testing, and a combination of the three. The committee finds that there are pros and cons of various approaches but leans toward tiered testing with the goal of focusing resources on the evaluation of the more sensitive adverse effects of exposures of greatest concern rather than full characterization of all adverse effects irrespective of relevance for risk-assessment needs. The committee, however, notes that tiered-testing approaches should be designed to expedite regulatory decisions and to discourage toxicity testing that is not used to address regulatory questions."* (NAS 2005).

20. In conclusion, I believe that there are sound, scientific data that demonstrate the adequacy of current risk assessment methods to protect human health,

including sensitive subpopulations such as the developing fetus, infants, and children. This fact, combined with the knowledge that hazard alone is not sufficient to characterize actual risk, would argue against a need to develop alternative regulatory approaches for chemicals when the concern is protecting children's health.

Laura M. Plunkett, Ph.D., DABT
April 29, 2008

REFERENCES CITED

Becker, R.A., L.M. Plunkett, J.F. Borzelleca, and A.M. Kaplan. 2007. Tiered toxicity testing: evaluation of toxicity-based decision triggers for human health hazard characterization. *Food Chem. Toxicol.* 45:2454-2469.

Brock, A. 1991. Inter and intraindividual variations in plasma cholinesterase activity and substance concentration in employees of an organophosphorus insecticide factory. *Br. J. Ind. Med.* 48:562-567.

Brown, D.R. 2001. Risk assessment around the country: A forum for risk information and analysis developed to inform regional, state, and local policy decisions. *Hum. Ecolog. Risk Assess.* 7:209-213.

Burin, G.J. and D.R. Saunders. Addressing human variability in risk assessment—The robustness of the intraspecies uncertainty factor. *Regul. Toxicol. Pharmacol.* 30:209-216.

Calabrese, E.J. 1985. Uncertainty factors and interindividual variation. *Regul. Toxicol. Pharmacol.* 5:190-196.

Calabrese, E.J. 2001. Assessing the default assumption that children are always at risk. *Hum. Ecolog. Risk Assess.* 7:37-59.

Charnley, G. and R. Putzrath. 2001. Children's health, susceptibility, and regulatory approaches to reducing risks from chemical carcinogens. *Environ. Health Perspect.* 109:187-192.

Dourson, M.L., S.P. Felter and D. Robinson. 1996. Evolution of science-based uncertainty factors in noncancer risk assessment. *Regul. Toxicol. Pharmacol.* 24:108-120.

Dourson, M.L. and J.F.Stara. 1983. Regulatory history and experimental support of uncertainty (safety) factors. *Regul. Toxicol. Pharmacol.* 3:224-238.

Ginsberg, G., D. Hattis, B. Sonawane, A. Russ, P. Banati, M. Koziak, S. Smolenski, and R. Goble. 2002. Evaluation of child/adult pharmacokinetic differences from a database derived from the therapeutic drug literature. *Toxicol. Sci.* 66:185-200.

Glaubiger, D.L., D.D. von Hoff, J.S. Holcenberg, B. Kamen, C. Pratt, and R.S. Ungerleider. 1982. The relative tolerance of children and adults to anticancer drugs. *Front. Radiat. Ther. Oncol.* 16:42-49.

Hattis, D., P. Banati, and R. Goble. 1999a. Distributions of individual susceptibility among humans for toxic effects. How much protection does the traditional tenfold factor provide for what fraction of which kinds of chemicals and effects? *Ann. NY Acad. Sci.* 895:286-316.

Hattis, D. P. Banati, R. Goble, and D.E. Burmaster. 1999b. Human interindividual variability in parameters related to health risks. *Risk Anal.* 19:711-726.

Hattis, D. 1987. Human variability in susceptibility to toxic chemicals—A preliminary analysis of pharmacokinetic data from normal volunteers. *Risk Anal.* 7:415-426.

National Academy of Sciences (NAS). 1983. *Risk Assessment in the Federal Government: Managing the Process.* National Academy Press, Washington, D.C.

National Academy of Sciences (NAS). 2005. *Toxicity Testing for Assessment of Environmental Agents, Interim Report.* Committee on Toxicity Testing and

Assessment of Environmental Agents, Board on Environmental Studies and Toxicology. National Research Council of the National Academies, National Academies Press: Washington D.C.

Naumann, B.D. 2001. Studies of categorical data-derived adjustment factors. *Hum. Ecolog. Risk Assess.* 7:61-106.

Nong, A. and K. Krishnan. 2007. Estimation of interindividual variability factor for inhaled volatile organic chemicals using a probability-bounds approach. *Regul. Toxicol. Pharmacol.* 48:93-101.

Pelekis, M., L.A. Gephart, and S.E. Lerman. 2001. Physiological model-based derivation of the adult and child pharmacokinetic intraspecies uncertainty factors for volatile organic compounds. *Regul. Toxicol. Pharmacol.* 33:12-20.

Plunkett, L.M. 1999. Do current FIFRA testing guidelines protect infants and children? Lead as a case study. Regul. Toxicol. Pharmacol. 29:80-87.

Plunkett, L.M., D. Turnbull and J.V. Rodricks. 1992. Differences between adults and children affecting exposure assessment. In: *Similarities and Differences Between Children and Adults: Implications for Risk Assessment.* P.S. Guzelian, C.J. Henry and S.S. Olin (eds.) ILSI Press, Washington D.C., 79-96

Rane, A. 1992. Drug disposition and action in infants and children. In: *Pediatric Pharmacology: Therapeutic Principles and Practice.* S.J. Yaffe and J.V. Aranda (eds.), Saunders: Philadelphia, 10-21.

Renwick, A.G. 1998. Toxicokinetics in infants and children in relation to the ADI and TDI. *Food Addit. Contam.* 15:17-35.

Renwick, A.G. and N.R. Lazarus. 1998. Human variability and noncancer risk assessment—An analysis of the default uncertainty factor. *Regul. Toxicol. Pharmacol.* 27:3-20.

Renwick, A.G., J.L. Dorne and K. Walton. 2000. An analysis of the need for an additional uncertainty factor for infants and children. *Regul. Toxciol. Pharmacol.* 31:286-296.

Sheehan, D.M. and D.W. Gaylor. 1990. Analysis of the adequacy of safety factors. *Teratology* 41:590-591.

Silverman, et al. 1999. Establishing data-derived adjustment factors from published pharmaceutical clinical trial data. *Hum. Ecolog. Risk Assess.* 5:1059-1089.

Skowranski, G.A. and M. Abdel-Rahman. 2001. Relevance of 10X uncertainty factor to the risk assessment of drugs used by children and geriatrics. *Hum. Ecolog. Risk Assess.* 7:139-152.

RESPONSE BY LAURA M. PLUNKETT TO AN ADDITIONAL QUESTION FROM SENATOR BOXER

Question. Plunkety during the hearing, you stated that, "as a scientist, I am not aware that some of those statistics are indeed true. " When I asked you which statistics. you answered, "Some of the statistics about the rate of cancer incidence increasing, the level that it has increased over the years. I think if you look at the literature. those numbers. at least the numbers that I am aware of are not supported by the scientific literature, at least. " Please answer the following questions concerning your statement:

Did you know that the National Cancer Institute. which is part of the US National Institutes ofHealth. states: "Over the past 20 years. there has been some increase in the incidence of children diagnosed with all forms of invasive cancer. from J1.5 cases per 100,000 children in 1975 to 14.8 per 100,000 children in 2004."

Did you know that the America Cancer Society, which has funded $3 billion in cancer research—including funding the work of 42 Noble Prize winners—estimates that "[s]ince the early 1970's, incidence rates of... (non-Hodgkin lymphoma) have nearly doubled. "

Response. Senator Boxer, I am aware of the sources you have listed above and in fact they are some ofthesamesourcesIreferredtoinmyletter ofMay 1,2008toSenatorInhofewhereI suggested that statistics for cancer incidence can be found in some reliable data bases such as the NCI. In that letter. I mentioned two documents that provide summaries of trends in cancer incidence over time available from NCI (e.g., Ries, L.A.G. et al. (eds). SEER Cancer Statistics Review, 1975–2005. National Cancer Institute. Bethesda. MD. http://seer.cancer.gov/csr/1975—2005/, based on November 2007 SEER data submission, posted to the SEER web site, 2008; Ries, L.A.G. et al. (eds). Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975–1995, National Cancer Institute, SEER Program. NIH Pub. No. 99–4649. Bethesda. MD, 1999).

As I stated, both of these documents are reliable, authoritative sources accessed by scientists when wanting to understand trends in cancer incidence in the U.S. I believe that review of these two documents reveals that the statistics cited at the hearing on April 29th are not supported by the NCI data. In general. cancer incidence overall has remained somewhat stable over the last 30 years, with some regional. age group. and racial variations. I would refer anyone interested in citing a cancer incidence rate to those sources. with one document specific to childhood cancers. I also believe that these two documents would be good resources for the Committee as they try to understand the incidence of cancer. As I do not know where your statistics above are actually derived from, as you have not provided me with the citations in your question above, I cannot respond specifically to your values. I would again reiterate, however, that the NCI indicate that the overall incidence of cancer has remained somewhat stable and that any trends in certain regional or age group statistics must be carefully considered in light of Ms. Heather Majors September 2, 2008 confounding factors such as changes in diagnostic criteria or screening? factors that often are responsible for purported increases.

RESPONSE BY LAURA M. PLUNKETT TO AN ADDITIONAL QUESTION FROM SENATOR INHOFE

Question. Dr. Plunkett, there appeared to be some confusion during the hearing about a comment you made about the "rate of cancer incidence increasing". I believe you stated:

"Some of the statistics about the rate of cancer incidence increasing, the level that it has increased over the years. I think if you look at the literature, those numbers, at least the numbers that I am aware of are not supported by the scientific literature, at least. I will end it there. " I believe you were making the point that the rate of increase may not be as great as others suggested, not that the rate was decreasing. Is this correct and please elaborate.

Response. Senator Inhofe, you are correct in your suggestion above regarding my statements. During the hearing it was erroneously asserted that I had testified that cancer rates in the U.S. are decreasing. What I was actually addressing in my testimony and answers to questions was the need to assure that any statistics on disease incidence that were presented at the hearing be based on sound science and not merely statements made for impact without a basis in actual scientific data. During the hearing I was concerned and raised questions when I heard statistics being mentioned that based on my experience, were not reflective of the actual incidences of cancer and the changes in sperm count in the U.S.

It is important to realize that data on something such as cancer incidence are complex. Statistics can be reported based on yearly incidence, incidence over time, incidence broken out by sex, age at diagnosis, mortality, etc. A scientist must consider whether any statistics collected are representative of the population of concern. The best source of such data for describing the U.S. population would be data collected in the U.S. Such an authoritative source would be the National Cancer Institute (NCI), which is a part of the National Institutes of Health, Department of Health and Human Services. Although I have not had time to do an exhaustive search of all the data available, there are several summaries of trends in cancer incidence over time available from NCI (e.g. Ries, L.A.G. et al. (eds). SEER Cancer Statistics Review, 1975–2005, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975—2005/, based on November 2007 SEER data submission, posted to the SEER web site, 2008; Ries, L.A.G. et al. (eds).

Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975–1995, National Cancer Institute, SEER Program. NIH Pub. No. 99—4649. Bethesda, MD, 1999). Both of these documents are reliable, authoritative sources accessed by scientists when wanting to understand trends in cancer incidence in the U.S. Review of these two documents reveals that the statistics cited at the hearing on April 29th are not supported by the NCI data. In general, cancer incidence overall has remained somewhat stable over the last 30 years, with some regional, age group, and racial variations. I would refer anyone interested in citing a cancer incidence rate to those sources, with one document specific to childhood cancers.

With respect to sperm counts in the U.S., there is no one source of data that I can point to for reference. However, one authoritative source, the World Health Organization International Program for Chemical Safety (WHO/IPCS), did perform a comprehensive review of the issue of endocrine disruption (including sperm count issues) in 2002 (IPCS. 2002. Global assessment of the state-of-the-science of endocrine disruptors. Geneva: World Health Organization). The WHOIIPCS concluded that with respect to the hypothesis that there may be a global reduction in human semen quality (including sperm count) that might be related to environmental exposures to chemicals acting as endocrine active substances, there is not a global trend for declining semen quality that can be identified based on considering all of the available data. They found that although some studies showed declines in certain regions or cities, other studies found no evidence of such decline, suggesting there may be regional trends but not a global trend. Therefore, this authoritative source does not support the statistic quoted in the hearing related to sperm count declines.

As I also stated in my previous letter, I strongly believe that science should not be used as a political tool to support one position or another, but should be used as part sofa decision making process. In this case, it is not sound science to use statistics that are not reflective of the appropriate population, or are reflective of only one study when there is body of evidence to consider.

Senator BOXER. We will get—it depends on the type of cancer, but we will get that information into, we will go to the Cancer Institute doctor and we will put those in the record. So wherever that will fall.

Dr. Lynn Goldman, we welcome you, M.D., Chair, Program and Applied Public Health at Johns Hopkins, former Clinton EPA Assistant Administrator for Pesticides and Toxic Substances. Also a pediatrician, I understand. We welcome you, a majority witness. Go right ahead.

STATEMENT OF LYNN R. GOLDMAN, M.D., M.P.H., PROFESSOR, ENVIRONMENTAL HEALTH SCIENCES, JOHNS HOPKINS UNIVERSITY, BLOOMBERG SCHOOL OF PUBLIC HEALTH

Dr. GOLDMAN. Chairman Boxer and members of the Committee, I really appreciate your interest in this issue. I think that the regulation of chemicals by EPA is a very important area.

In 1976, when the Toxic Substances Control Act was passed, there were great hopes by Congress for what it might do. Unfortunately now, 32 years later, one must acknowledge that this Act needs to be revised, in particular, to protect children. Chairman

Boxer, I know that you have had a major role in legislation to protect the health of children. Your colleague, Senator Lautenberg, talked about the Kids Safe Chemical Act, which I think has been a wonderful effort.

I understand, as a former regulator of the chemical industry, the way that chemicals play a vital role in the economy. They are very important in our society and I would not underestimate that. But I think I also understand that strong regulation is needed to assure the health of all our citizens, especially our children.

Today I am here to address the concerns about EPA's IRIS program. What is this program about? It was mentioned earlier that the dose makes the poison. What IRIS is about is establishing what that dose is that makes the poison, so that everybody in society, whether it is regulators, doctors, States, industry, will know what EPA's views are about that does. I don't think any of us here today are saying that any level of exposure to any chemical is of concern. We want to know what the levels that are safe and what levels are of concern. That is what IRIS is all about.

I have been studying formaldehyde, and I think it is an example that helps to understand about why this is important. You know that formaldehyde is used extensively in the manufacture of wood and wood products. For many years, it has been considered to be a probable human carcinogen. But in 2006, IARC, the International Agency for Research and Cancer, made a determination that formaldehyde is known to cause cancer in humans, does actually cause cancer in humans. This is a very difficult threshold of evidence to meet for any chemical.

And the truth is that nearly everybody but the United States has taken strong regulatory action on formaldehyde. The State of California, the European Union, Australia, Canada and Japan have mandatory standards that are several fold stronger than the U.S. Government's voluntary standards for formaldehyde in wood products.

Since 1997, the EPA has been trying to reassess formaldehyde. In 2004, this process was brought to a halt. Basically, EPA's political leadership was convinced that new science was right around the corner and they should delay a new IRIS listing for formaldehyde. At the same time, the Chemical Industry Institute of Toxicology, the CIIT, published its own risk assessment, which would say that formaldehyde standards should actually be weakened and not strengthened.

It was fairly unprecedented. In 2004, when EPA's Air Office issued its new hazardous air pollutant standard for formaldehyde, it actually incorporated the CIIT assessment without any concurrence from EPA's scientists or from EPA's science advisory board. Now, I should say that rule was struck down in 2007 for procedural problems, other problems with the rule. But I think that this shows how, even in EPA's actions, this lack of progress with IRIS has been a problem.

Then in 2005, Hurricanes Katrina and Rita flooded the Gulf Coast, and as you know, FEMA provided 120,000 travel trailers to the victims of those storms to serve as temporary housing. Unfortunately, these trailers contained unacceptable levels of formaldehyde. I think the story is very familiar to all of you, including the

slow response by the Federal Government, the tragic consequences to the people who were living in those trailers, all of which in my view would have been unnecessary if EPA had done the right thing in the first place in terms of moving forward an appropriate scientific assessment.

My point is that when you suppress this kind of information about what is the dose that makes the poison, there are serious consequences. We need to have an EPA whose scientists are free to communicate to us about risks. That is very, very important. When they are not free to do so, when there are impediments, when they are held hostage to these processes that go on interminably, the public's health does and will suffer.

It is a complex and challenging process to do these IRIS reviews. It is also difficult to peer review these. The process of peer review needs to be done——

Senator BOXER. You will have to conclude.

Dr. GOLDMAN. I will. It needs to be done in a scientific process and not through a process that is basically an invitation to back door involvement by parties who might be affected by the scientific assessment. I think that is what we have here.

Thank you very much.

[The prepared statement of Dr. Goldman follows:]

Testimony
Oversight on EPA Toxic Chemicals

Senate Environment and Public Works Committee
Lynn R. Goldman, M.D., M.P.H.

Professor, Environmental Health Sciences,
Johns Hopkins University, Bloomberg School of Public Health
April 28, 2008

Chairman Boxer, Senator Inhofe and members of the Committee on Environment and Public Works, it is my honor to testify today about the US Environmental Protection Agency (EPA) and its efforts to manage toxic chemicals. With your permission I would like to submit my full testimony for the record.

I am a professor of environmental health at the Johns Hopkins Bloomberg School of Public Health. From 1993-98, I served as Assistant Administrator for Prevention, Pesticides and Toxic Substances at the US EPA Prior to that I worked for eight years in public health with the California Department of Health Services. The views I convey today are my own.

When the Toxic Substances Control Act (TSCA) was passed in 1976, there were great expectations that it would improve our understanding of chemical risks and manage these risks to protect human health and the environment. It is now 32 years since the enactment of TSCA. Unfortunately, this statute fails to provide EPA with the authorities that it needs to identify chemical hazards and to take decisive actions to manage risks. In particular, there are no specific provisions to protect children and other vulnerable populations. Chairman Boxer, I know that you have had a major role in enacting legislation to protect the health of children. I also appreciate the approach that has been taken by Senator Lautenberg and others on this committee to draft legislation to reform TSCA, in order to address this very serious weakness in EPA's authority. Chemicals play a vital role in the US and world economy, and to human welfare. Strong regulation is needed to assure the health of all our citizens, especially our children.

Today I am here to address more recent concerns with EPA's management of chemicals. I will make two points. The first is that suppression of scientific information about chemicals has real consequences to public health. The second is that the new changes to EPA's Integrated Risk Information System (IRIS) are counterproductive.

I am completing a study of one particular chemical, formaldehyde. I am going to start with the formaldehyde story because I think it illustrates the problem we are facing today. Formaldehyde is one of the most well characterized chemicals in the world. It has serious acute and chronic toxicity. Most of the formaldehyde produced today is used in wood products such as particleboard, plywood and veneer. For years formaldehyde has been considered a probable human carcinogen, but in 2006 the International Agency for Research in Cancer (IARC) determined that newer evidence supports classifying it as a known human carcinogen. IARC concluded that there is sufficient evidence that formaldehyde causes nasopharyngeal cancer in humans, "strong but not sufficient evidence" for causing leukemia in exposed workers and limited evidence it causes sinonasal cancer. As evidence has accumulated, many countries, and the state of California, have proposed strict enforceable standards for formaldehyde in buildings; the California standards are 3-4 times more stringent than the voluntary standards that have been adopted by the Consumer Products Safety Commission. California's standards are consistent with those in Europe, Australia, Canada and Japan.

For years, the scientists at the EPA have been trying to update the agency's assessment of formaldehyde on IRIS. In 2004, this was nearly complete, but the process was postponed. The formaldehyde industry persuaded members of Congress and the EPA's political leadership that "new" scientific findings would soon be forthcoming, justifying a delay. At the same time, the CIIT (Chemical Industry Institute of Toxicology) published its own formaldehyde cancer assessment. In an unprecedented action, in 2004 EPA incorporated the CIIT assessment into its fiberboard hazardous air pollution rule, without the concurrence either of EPA's scientists or the EPA's independent Science Advisory Board (SAB). Over the last five years no new scientific publications have emerged that would alter the formaldehyde listing on IRIS. Numerous published papers have disagreed with the CIIT assessment. Unfortunately, in 2005, Hurricanes Katrina and Rita flooded the Gulf Coast, and thousands were left homeless. FEMA rushed orders for 120,000 travel trailers, which, as we all know now, contained significant quantities of formaldehyde. The first complaints of formaldehyde-related symptoms among trailer residents surfaced in February 2006. You know about the rest of the tragedy; and the slow response to the problem by the federal government.

My point is that efforts to suppress science have real consequences for the protection of public health. With increasing frequency EPA's scientists tell me about impediments to doing their jobs. Like formaldehyde, several other major chemicals under assessment by the EPA, like the dry cleaning solvent perchlorethylene, also have been held hostage. The new process has nearly ground EPA's efforts on IRIS to a halt. Withholding information about chemical hazards does cause harm to the public. EPA leaders must stop suppressing and delaying IRIS listings and other scientific efforts.

The assessment of a toxic chemical like formaldehyde is a complex and challenging process that involves scientists with specialized training in a myriad of disciplines related to toxicology and epidemiology. Depth of expertise is required in many specific areas. The peer review for such an assessment is even more challenging; not only a broad array of expertise but also a higher level of proficiency is required. This is the role – appropriately – of the EPA Science Advisory Board. Another time-honored mechanism for scientific input to EPA is through processes like the National Toxicology Program, which promote scientist-to-scientist collaboration about toxic chemicals.

OMB's new role and the new interagency review process for IRIS are terribly misguided. With all due respect to the people at the OMB, their small complement of scientists is not likely to add value to these assessments. Even worse, the new process is an open invitation for interested parties to meddle with IRIS in secret. First, certain federal agencies, like the Department of Defense, are responsible for waste cleanups and have a direct financial stake in EPA's toxicology assessments. Like all responsible parties, they deserve a transparent process so that they can track EPA's thinking about chemicals and provide input at certain points in time. However, it is completely unacceptable for them to have even an appearance of a veto over EPA's scientific conclusions. Additionally many federal agencies are charged by Congress to promote industry and commerce. Their involvement in the IRIS interagency process gives appearance (if not the reality) of providing a back door through which industry groups

can exert pressure to modify EPA's conclusions or to subject the process to endless delays. In contrast, when the EPA's Science Advisory Board considers an IRIS listing, all parties, nongovernmental and governmental, are able to provide input in open meetings. The members of the SAB evaluate this input based on scientific merit, not politics. The net effect of this change in the IRIS process is to undercut the scientific credibility of the IRIS listings. It undermines the public's trust in the EPA. In other words, it injects political science into EPA's IRIS process.

This is a pivotal time. There is a rising tide of chemicals regulation by states. However, most states do not have sufficient resources to manage chemicals and must rely on EPA. Chemicals play a vital role in our economy but we must manage them well. As we have learned in the context of automobiles, continuing to rely on outdated and polluting older technologies can be harmful to human welfare as well as human health. Finally, in the case of chemicals, what you don't know *can* hurt you. Many people in public health, in state governments and in industry need to know about EPA's assessments of these chemicals. Let's allow the science to be the science; the new IRIS policy should be rescinded immediately and the work of EPA's scientists should be made available for peer review and publication. In the long run, overhaul of TSCA to strengthen our protections from health hazards of toxic chemicals. Meanwhile, EPA needs to act with prudence and to fulfill its duty to protect the health of the public and the environment.

Senator BOXER. I think that is the nub of what we have here. Thank you.

Here is what we are going to do. I am going to give Senator Whitehouse and Senator Barrasso 7 minutes each to ask their final questions and sum up, and then I will take my turn and then we certainly thank this panel and the one before. This has been a very important hearing.

Senator, 7 minutes, please.

Senator WHITEHOUSE. Thank you very, very much, Chairman.

Let me start by asking Dr. Goldman about the, you described it as a back door process or a back door that the IRIS program creates in the process for influence by people who aren't proper scientists. I agree that it appears to deliberately create a vector for political interference. To what extent it will be used or not is open, but epidemiologically, you don't want to create that kind of vector, if you can, even in a political environment.

But in response to that, Mr. Gulliford suggested that OMB had scientists on staff and that raised the implication that what is happening here with OMB is that they are adding to the science knowledge that EPA possesses. Based on your experience, how would you rate the scientific, particularly the science of chemistry, knowledge that is contained within OMB compared to that is contained within EPA with respect to the chemical process and its approval for use around humans?

Dr. GOLDMAN. For any one chemical, it is difficult to construct a panel of scientists who are qualified to peer review an assessment like the IRIS assessment. I cannot think of a single small group of scientists who are qualified to peer review each and every one of those, in addition to all the other science that the scientists at OMB supposedly are reviewing. No matter how good they are, it is not possible for them to have the depth and the breadth that you need to do that kind of review.

How you add value through peer review is through something like the Science Advisory Board that EPA already has, which, by the way, is done out in the open. Those reviews are in the sunshine. Anybody can come and contribute, industry can contribute, others can come and contribute. And their arguments are considered on the merits, in terms of the science they are presenting. It is not political science. This is about science and the science advisory board process is the best way to accomplish that.

Senator WHITEHOUSE. Are you comfortable with the IRIS process as proposed at all?

Dr. GOLDMAN. Not at all. And I am very disturbed by the GAO report and seeing that EPA has increased the resources for that program fivefold over the last several years, with what looks to me to be about a four to fivefold decline in productivity. And now they are proposing to put more bells and whistles on the process. If nothing else, it is just poor management. There is very little output. More than half of the listings are out of date. And this is information that everybody needs, including industry.

Senator WHITEHOUSE. You mentioned formaldehyde, which is of particular interest. The Chairman knows very well my wife, I am a very over-married human. And as she well knows, my wife is a trained scientist. As a result of her education and the work she did

as a marine biologist, she has had substantial exposure to formaldehyde. So that is, you ring a bell with me when you talk about formaldehyde.

As I understood it, you said that the EPA began its process to evaluate the carcinogenic effects of formaldehyde back in 1997. And it wasn't until 2004 that the process was closed to completion. It was then derailed by a finding, I guess by the Administrator himself, that there was new science around the corner.

Was there any new science around the corner, or was he just waiting for the CIIT assessment? Was there, in the world of this science, was there some sort of tectonic shift that took place? Was there a new development that emerged?

Dr. GOLDMAN. Nothing has emerged since then. You are married to a scientist, so you know there is always new science around the corner. What one has to be committed to is periodic reevaluation, so that new science is incorporated. But no, nothing new has emerged since 2004, nothing.

Senator WHITEHOUSE. And then you said it was struck down in 2007. Struck down by courts?

Dr. GOLDMAN. The rule was struck down, but not because of the risk assessment, but because of other things, such as some of the exemptions they tried to include.

Senator WHITEHOUSE. The Chairman has hosted hearings on the EPA batting record in the courts of this Country with their theories of why various anti-environmental policies should stand up. But here we go again. So as I summarize it, here we are in 2008. They started in 1997. Because of all this various folderol, we are effectively no place right now with respect to formaldehyde. How would you describe where we are in the process right now with respect to making a conclusion as to whether it is carcinogenic and what steps should be taken to protect public health?

Dr. GOLDMAN. I think we have to rely on the international assessment that came forth from IARC in 2004. We still don't have a voice from EPA on this. As far as I can tell, we are going to wait a long time before we will hear from EPA unless something is done to change this process.

Senator WHITEHOUSE. Thank you.

Dr. Giudice, I would like to give you the opportunity to respond to Dr. Plunkett, who suggested in her testimony that the statistics that you shared with us were not supported by data. Just based on your resume, as the professor, indeed, Chair of the Department of Obstetrics, Gynecology and Reproductive Sciences at the University of California in San Francisco, I am not inclined to believe that you have made up statistics here in testimony before a Senate Committee. But I would like to give you the chance to buttress your assertions in light of her comments.

Dr. GIUDICE. Thank you. I appreciate that opportunity.

There is a reference by Bray and colleagues at the International Journal of Cancer in 2006, volume 118, pages 3099 on trends in testicular cancer incidence. This is very recent and I would suggest that our colleagues look at that particular article.

I am happy to provide the Committee with the written references for the other statistics that I quoted. Thank you.

Senator WHITEHOUSE. Madam Chair, thank you very much.

Senator BOXER. Thank you.

Before I call on my colleague, I want to put two things in the record, or three things. First, letters from more than 50 national, State and local public health and environmental organizations expressing their opposition to the new interagency policy on IRIS, and also I am putting in, if there is no objection, recent news reports on this issue. Then second, Senator Whitehouse before you leave, this is in reference to your question and also the assertion by Dr. Plunkett that cancer is going down.

How have childhood cancer incidence and survival rates changed over the years, National Cancer Institute, an increase over the past 20 years of children diagnosed with all forms of invasive cancer, from 11.5 cases per 100,000 in 1975 to 14.8 cases per 100,000 children in 2004. And finally, also from the Cancer Institute, lymphoma, an estimated 74,000 new cases of lymphoma will occur in 2008. Since the early 1970's incidence rate for non-Hodgkins lymphoma has doubled. Just wanted you to know that before you left.

[The referenced material was not received at the time of print.]

Senator BOXER. Senator.

Senator BARRASSO. Thank you very much, Madam Chairman. I have two documents I would also like to read into the record, if I could, one from Synthetic Organic Chemical Manufacturers Association and another from the National Petrochemical Refiners Association.

Senator BOXER. Without objection, Senator.

[The referenced materialwas not received at the time of print.]

Senator BARRASSO. Thank you.

Ms. Gellert, I appreciate your comments and your testimony as you are a cancer survivor, with placental cancer. My wife is a cancer survivor of breast cancer, which is obviously much more common, one in eight women, than placental cancer. Dr. Giudice, you are the professor. Placental cancer is fairly rare, isn't it?

Dr. GIUDICE. Placental cancer is very rare, yes. It is much more common in Asia than it is in the United States. And the prevalence here I believe is something like 1 in 10,000 to 15,000.

Senator BARRASSO. I think it is Taiwan with the greatest prevalence that I have studied, is it thought to be environmental in Taiwan?

Dr. GIUDICE. It is unclear what the etiology is.

Senator BARRASSO. All right. I was curious how that all came about. Thank you.

I notice that the two of you work pretty closely together. You are on the board of advisors of the UC San Francisco Medical center—no? All right. Then I must have a different Annette Gellert that is listed for the WELL Network.

Ms. GELLERT. I am a previous board member of the Obstetrics and Gynecology Research and Education Foundation at UCSF. That was a previous position. I am not currently on that board.

Senator BARRASSO. You are currently off the board.

Ms. GELLERT. I actually came to know about that board when I was at UCSF getting treated for the molar pregnancy that I had. My point was that I really, I don't know what caused it. I want to

know what caused it. I want to know, I want more information so that I can, I want to know about my husband, too.

Senator BARRASSO. With his bladder cancer? My best thoughts are with him.

Ms. GELLERT. Yes. The known cause of that is industrial chemicals from every source that I could find.

Senator BARRASSO. And other causes, there are other——

Ms. GELLERT. Well, smoking, and he has never smoked a day in his life. Two risk factors are mentioned, one is smoking and the other is industrial chemicals.

Senator BARRASSO. OK. And then I understand, Doctor, that you are also an honorary board member of WELL Network?

Dr. GIUDICE. I am. I just became, and when Ms. Gellert was on the OB/GYN Foundation Board at UCSF, this is close to 20 years ago, and I joined UCSF two and a half years ago.

Senator BARRASSO. Thank you.

Dr. Plunkett, I think we had kind of a back and forth, people responding to differences. Are there additional amounts of my time you would like to use to help clarify some of these matters?

Dr. PLUNKETT. I just wanted to State that I am not asserting that cancer rates are going down. What I was trying to comment on was the fact that actually, I heard Ms. Gellert mention some statistics on rates and incidence. I had not, I am not aware of those particular numbers. I am concerned because I think there is a perception of the lay person and the public, and there is information out there that the scientists are aware of, and maybe we as scientists need to be better at getting that information out, so that the public is aware of what the real risks are, and what true incidence rates, what is the real incidence rate, how do you calculate it, how do you determine it, versus the numbers that may get thrown around in the popular press. That is all. That is really what my comment was about.

I am not aware of the data that would support some of the numbers that were coming out. Certainly if there is such data, I would love to see it. I am just not aware of it. I am also not aware of the fact that the incidence rates have been going up to the level that has been asserted. That was the comment or the position I was trying to take.

Senator BARRASSO. You said in your testimony that the EPA currently has in place some methods for considering infants and children as separate exposed populations, apart from adults, allowing a risk assessment to consider and account for differences in exposure patterns. Could you elaborate a little bit on that?

Dr. PLUNKETT. Yes. In the current methods that are used, where you do a risk assessment, you are looking at all the potential populations that can be contacted or exposed to the product. And if you have a product or chemical where you are worried about child exposure, such as if you had an infant, a bottle for an infant or you had some other product that the child might be contacting routinely, you can do child-specific exposure assessment on that. In addition to that, in the toxicity evaluation part of the risk assessment, for many, many chemicals you have data that has been collected in developing animals, reproductive and developmental toxicity studies,

where you actually can assess what were the direct effects on a developing organism from exposure to that chemical.

I know there are many chemicals that may not have that kind of data. But most of the ones we are talking about that have been raised at issue in this hearing, as I have heard it, are ones where that data is available.

Senator BARRASSO. Mr. DeLisi, you talked about the program in Europe, the REACH program. Is there a lot of hazard and exposure data available that has been gathered from that on different chemicals already?

Mr. DELISI. Nothing has been gathered yet. The pre-registration period starts on the 1st of June, then you have until 2010 for more than a thousand tons a year of commerce and 2013 for a hundred to a thousand and then 2018 for less than a hundred tons.

Senator BARRASSO. If we don't have any data yet from that REACH program, is it right to make comparisons between TSCA and the REACH program?

Mr. DELISI. I don't know how that would be possible.

Senator BARRASSO. I want to ask about some potential, Mr. DeLisi, in making the change in TSCA so that it shifts the burden of proving safety from the EPA to manufacturers. Would you recommend shifting that burden and how will that affect a manufacturer's ability to meet its needs of customers?

Senator BARRASSO. The burden needs to continue as it is, which is really shared. I was at a REACH conference last week, because REACH does talk about banning products, and frankly, the thing that most startled me was a representative of Rolls Royce trying to figure out how they could make a jet engine altogether without the use of nickel compounds, which could potentially occur in the EU, that nickel compounds would be banned. He literally said that, we can't figure out how to keep a jet engine together without the use of those kinds of materials.

Senator BARRASSO. Thank you, Madam Chairman.

Senator BOXER. Well, we are going to close this panel out, and we have a few comments, a couple of questions.

This has been a really important and far-reaching hearing. I want to thank each and every one of you. I think it has been good to have both sides on this panel. And frankly, on the other panel as well, the GAO saying that they investigated the EPA and found out politics is taking over the program, and EPA saying, oh, no, nothing could be further from the truth. Well, let's let the public judge and let's let my colleagues judge.

But let me tell you what is going to happen, Mr. DeLisi and Dr. Plunkett, Ph.D. If we don't see action out of the EPA on listing these harmful chemicals, not only listing them but regulating them, Congress is going to do it. Senator Feinstein offered an amendment with me to ban phthalates. It passed overwhelmingly. You can see where Senate Whitehouse is coming from on formaldehyde.

So don't think because you may be looking at this process, the weaker it gets, the stronger we are going to get. Because no Senator in the light of day, I shouldn't say no, most will not be able to take the heat of these dangerous chemicals. People are not stupid, they are smart, they understand, they see what is happening

to their families. No one can tell them what is happening to their families, because they see it.

So no one can say, oh, it is safe and cancer is going down or whatever you said, I am checking on your words. The fact is, we know the facts. Childhood cancer, up. I mean, it is a fact.

So I just want to thank the doctors on the panel, the medical doctors on the panel. You took an oath to do no harm. And what you are doing through your work, your active work, which I praise so much, what you are doing is making sure that we are not harmed.

And what is so intriguing about this hearing is that there are several issues raised, which is what we wanted. One is the current system, the way we regulate chemicals now and how it has failed us and how they have come up with four decisions when they were supposed to come with a hundred in the last 2 years.

So it has failed us, because the Administration has informally put into place the change in the IRIS program where they are allowing people to sit around a table secretly and give their views. And they have tainted and corrupted, and I use my words advisedly, they have corrupted the process of risk assessment. And the point is, it is not going to work, because the people won't allow it to happen.

And you know, we met with a chemical company the other day who said that they are, and I am going to just tell you what happened, and I will direct this to Mr. DeLisi. We met with a chemical company that said they have invented substitutes for toxic chemicals, such as insulation without formaldehyde. And without strong regulations on the chemicals that present a risk, there is not a strong market for the safer product.

So would you agree that sometimes regulation will spur invention, the genius of America, which is what Annette Gellert talked about, working with the private sector? Why is it my colleagues on the other side paint this picture of, every time we want to help the people of America get safer, oh, we are going to hurt the economy? That has never been true with environmental regulation. Never. We have had green industries, we have had green jobs. This is the scare tactics. So people get sick and they die and oh, we can't do anything about it, because it is going to hurt people's jobs. Well, you know, if you are really sick and you can't breathe, you can't come to work. Pretty basic.

So Mr. DeLisi, I want to ask you, don't you think that when there is reasonable regulation that it presents an opportunity for business to come up with a safer product that you could then export to Europe, where there is obviously going to be a huge market for greener products? What do you think?

Mr. DELISI. Senator, unfortunately, I think it is a two-edged sword. My Senator, Frank Lautenberg, this morning mentioned DDT. DDT is still in use in sub-Saharan Africa and lots of places, protecting people from the ravages of the mosquito-borne diseases. I would not want to be a regulator——

Senator BOXER. OK, I am not asking you about DDT, because I know that story is always brought up. I am asking you about this man who came in from a chemical company and said they are ready to roll with a substitute for formaldehyde. I am asking you,

yes or no, is there ever a case where reasonable regulation will lead to better, safer products? Yes or no?

Mr. DELISI. It can.

Senator BOXER. Good.

Mr. DELISI. But if the cost of that insulation that he is producing is so large that nobody can afford it, that is a down, that is a problem for the consumers.

Senator BOXER. Yes. But if I told you that your kid being exposed to certain levels of formaldehyde is going to get lung cancer, that the chances are, it is a very good chance, don't you think that is something we ought to move on and allow these substitutes? Don't you think that people in the Katrina housing there deserve to have accommodations that were free of formaldehyde? Don't you think?

Mr. DELISI. I am not an expert in formaldehyde, but if that has been proven, absolutely.

Senator BOXER. Good. Well, we are working on it, here, we are getting there. I love agreement.

Well, let me just say, again, do we have this? OK. All right. So we are going to put a lot of studies in the record, we will leave the record open for a week. And in summing up, here is where I think we are. We have an IRIS process that is the basis for many of our various environmental laws. That is how they, the Clean Water Act, the Safe Drinking Act, the Superfund, TSCA, they rely on—did I leave anything out?—Clean Air Act, they rely on the IRIS program. So IRIS cuts across.

Now, we know the IRIS project has been corrupted. And the reason we know it is the GAO did an investigation and they are telling us that already, even without the new system in place, in effect, everything has basically stopped. And instead of listing and regulating 100, not listing, scratch that, instead of regulating 100 chemicals over 2 years, they have regulated four. So we are in a crisis. Annette Gellert was right, she used that word. We are in a crisis.

If this goes forward, this process that Mr. Johnson, who refused to come here, somebody said no wonder he went to Australia, he doesn't want to sit across from me, I totally get it. But the fact of the matter is, he has a responsibility to be here and defend himself on this. This is a nightmare. This is a scandal.

So we now have a circumstance where we are going to see a formalization of a process that puts politics in the center of regulating chemicals as Dr. Goldman alluded to, instead of pure science. This is a travesty. And it is happening under our noses.

We are not going to stand for it. Either we are going to change things in the election or we are going to start banning these chemicals. Because there isn't one colleague that I know who is going to be able to stand the heat when there is proof about these chemicals.

Now, I know Dr. Plunkett, you have defended people, your firm has, when they are sued, is that right?

Dr. PLUNKETT. Most of my litigation work currently is in plaintiff's litigation, actually, not in defense.

Senator BOXER. OK, so you bring suits against chemical companies?

Dr. PLUNKETT. I don't bring suits. I have been an expert witness in litigation where suits have been brought against mainly pharmaceutical companies for injuries related to——

Senator BOXER. So you have testified for the injured party?

Dr. PLUNKETT. Yes, I have.

Senator BOXER. Or for the company?

Dr. PLUNKETT. For the inured party, in most cases.

Senator BOXER. You do. So your firm is bent toward making sure that people who are injured by chemicals have a right to sue, and you come in and you testify on behalf of the injured person, is that correct?

Dr. PLUNKETT. I act as an expert witness, to tell you what I do, I act as an expert witness, provide pharmacology and toxicology and FDA regulatory testimony related to the risks and hazards posed by a drug and whether or not that drug could have caused the injury in an individual.

Senator BOXER. OK, well, I have some confusion, because your firm advertises, I have seen the advertising, that you would represent business in defending them. And you are saying you defend the plaintiffs, the harmed ones.

Dr. PLUNKETT. I have worked on both sides. I have also done litigation where I have worked on behalf of industry as well. But in expert witnessing, currently in my litigation practice, all of my cases are plaintiffs cases at this point in time.

Senator BOXER. OK, but, this firm——

Dr. PLUNKETT. Integrative Biostrategies, yes.

Senator BOXER. So this is wrong, it says it represents product liability, toxic tort, heavy metals, petrochemicals, pesticides and that is, my understanding is that they support the companies. That is not right?

Dr. PLUNKETT. I do work on behalf of chemical companies in risk assessment and regulatory issues, yes.

Senator BOXER. Oh.

Dr. PLUNKETT. I have also worked on behalf of individual, for example, cities, other entities outside of industry. So I do both of those things.

Senator BOXER. So cities that are sued?

Dr. PLUNKETT. No. It is not all litigation work. In fact——

Senator BOXER. Let's give an example of a city you have represented.

Dr. PLUNKETT. For example, I have not represented, I have worked on behalf of a small city in Texas where there was a lead battery recycling facility located in town, right within the town. I worked with the city to help do a blood lead study on whether or not the industry was impacting the residents. I designed the study and helped implement the study for the city. So in that case, I was working on behalf of the children and the families within the city to determine whether there was a risk to their health.

Senator BOXER. Well, good for you. Because then you ought to know about childhood cancer rates a little more.

Dr. PLUNKETT. I——

Senator BOXER. Here is the thing. We are dealing with life and death here. We have a witness who is experiencing a spouse who has bladder cancer. She said the two causes that she has been able

to learn, because they don't know why, are smoking, which he never did, and exposure to industrial chemicals. We need to find out these things. We need to know, frankly. Our Government needs to know, so you don't have to go off to Texas and figure out what this, I mean, we ought to have the information of what these batteries do.

Dr. PLUNKETT. I would agree with you, Senator, that we need to know about the chemicals. My only point, the reason I am here today is to say that I believe there are risk assessment methods currently in place that allow us to determine which chemicals truly are risks, based on hazard information which we have, but also exposure and the actual information from the science on the responses in individuals.

Senator BOXER. Right. And I will tell you, what we have in place is the IRIS program.

Dr. PLUNKETT. We have more than that in place, I would argue.

Senator BOXER. That is the basic, well, you could argue it. But the fact is, every single agency has told us that the IRIS program is the program that is the basis for their decisions, OK? So the IRIS program is the basis for regulation under the Clean Air, Clean Water, and Superfund and all the things that I mentioned before.

So the IRIS, the integrity of that program is at stake here. That is why, when the GAO tell us the program is a shadow of its former self, now, to get to the issue of REACH is very important. Because, Mr. DeLisi, I want you to explain something to me. My understanding is a lot of chemical companies do business in Europe. Is that correct, would that be your understanding?

Mr. DELISI. Yes.

Senator BOXER. And they will have to conform with REACH, is that correct?

Mr. DELISI. Or they can make a decision to stop doing business in Europe.

Senator BOXER. Exactly. And what do you think people will do? Do you think they will walk away?

Mr. DELISI. Some will.

Senator BOXER. Well, I would argue they won't walk away. I will argue that they will want to, because this is a global marketplace. And with the dollar falling as it is, this is the moment where our business are really, at least beginning to see an increase in their exports. So I would argue that they would.

And I would further say, going back to my initial point, that when we have this concern, and it is expressed in legislation, you are going to have an impetus for these substitutes. Now, you are very right, maybe they will cost a little more. I would submit to you, if you ask the American people, if you could reduce the rate of childhood cancer, we could go into what those cancers are, by taking the following steps, having to pay 35 cents more for a solvent, or a dollar more for a different type of cleanser, I would be people would be glad to do that.

So from my perspective, I think it is very shortsighted for business to put their head in the sand and act as if nothing is going to change. Because here is my point. If we don't see a coming together here and I will get back to what Annette Gellert said, which

is, working together with business and Government and the nonprofit community, if we don't see that happening, I am just saying, colleagues of mine are going to take matters into their own hands and you are going to see banning of these chemicals and banning of these products. And you will not know what is going to hit you next.

So I think it is in the best interest of business to work with us in a way where we do have an open, transparent process here, where we don't have the regulation of a chemical such as formaldehyde get bogged down, as Dr. Goldman said, when we were just there at coming up with the regulation, Mr. Johnson pulled it down. That is not going to sit well, and you are going to be far worse off. You are going to have no certainty because you are going to have people going to the floor of the Senate saying, my community, so many people got this type of cancer. And you are going to really have more of a problem.

So I would urge us to work together. I think the message of the Wellness Foundation, is it the Foundation?

Ms. GELLERT. The WELL Network.

Senator BOXER. The WELL Network. That is a great message. We are all in this together. This shouldn't be one side arguing with another. We have everything to gain when we have safe products. We have a confident community that won't start boycotting certain products. And I just think do no harm is our first thing we should think about, do no harm. But second, make things better.

I think we ought to look at what Europe is doing. I think we ought to realize that it is in the best interest of our businesses to learn to work with these restrictions and see how we can have a system, frankly, that isn't different. Because I think that another thing Annette Gellert said is right on the mark, we don't want America to be the dumping ground for dangerous products.

Because here is what is going to happen, I will tell you right now, our people will start importing products from Europe in numbers. And by the way, it will be a big business. Somebody will get a license, they will bring in these safe products and you will not be able to compete because the American people understand that some of these chemicals are dangerous. And if they have an opportunity to buy a green product, they are going to do it.

So I think this could be a win-win for business if we have a little bit of a different attitude. Otherwise, you are going to have competition from abroad you never thought you had. I just think that is not good for business and it is not good for our people. So this has been a heart-felt hearing. I really thank all of you for being here, all of you, with your perspectives. I respect all the perspectives, but I think at the end of the day when our people are healthy, we are a better Nation for it.

Thank you very much, and we stand adjourned.

[Whereupon, at 12:35 p.m., the committee was adjourned.]

STATEMENT OF HON. BENJAMIN L. CARDIN, U.S. SENATOR FROM THE STATE OF MARYLAND

Madame Chairman, thank you.

The mission of the Environmental Protection Agency is to protect human health and the environment. The Integrated Risk Information System (IRIS) Program is

a manifestation of that part of the EPA's mission which includes the evaluation and regulation of toxic chemicals.

With over 500 chemicals listed, and over 9,000,000 queries to the IRIS data base, IRIS is a valuable resource both within the U.S. and around the world in understanding the potential human effects that exposure to the listed chemicals might cause. The quantitative information contained in IRIS allows IRIS to be a component in the regulatory process of many states and even other countries. The regard with which this data base is held is a tribute to the tireless efforts of EPA scientists in evaluating the risks of the listed chemicals. In order to be both useful and credible, the process to list a chemical in the IRIS data base must be unbiased, science-based, timely, and transparent.

In the last few years, despite increases in IRIS personnel, a backlog of IRIS assessments have developed. This backlog is due, in part, to new OMB-managed, interagency reviews and due to delays in completion of assessments to await new research.

Earlier this month, the EPA released a revised assessment process for IRIS. This revised process concerns me as it will allow far less transparency into the decision making process.

The new assessment process conflates the EPA's science position on an assessment with the EPA's science policy position. Assessment findings should inform policy, not be informed by policy.

Finally, this revised assessment process continues the recent practice of OMB's having a role in the process as well as establishing a new, interagency review process for IRIS. This change potentially compromises the integrity of IRIS by allowing those agencies that may have a stake in the EPA's assessment be able to influence that very assessment.

I am pleased to welcome Dr. Lynn R. Goldman, a professor of environmental health at the Johns Hopkins Bloomberg School of Health. Dr. Goldman has served as EPA Assistant Administrator for Prevention, Pesticides and Toxic Substances. Dr. Goldman's work in reducing the risk of chemicals and pesticides to the health of the public in general, and children in particular, is noteworthy.

I look forward to hearing Dr. Goldman's testimony and that of all of the other panelists today as we conduct this oversight hearing into EPA's toxic chemical policies.

Public health and environmental policy decisions must be rooted in objective scientific assessments. These assessments must be timely and made using the best practices possible.

Thank you Madame Chairman.

BEFORE THE
SENATE COMMITTEE ON ENVIRONMENT AND PUBLIC WORKS

STATEMENT FOR THE RECORD OF THE
AMERICAN CHEMISTRY COUNCIL

May 5, 2008

I. Introduction

The American Chemistry Council (ACC) appreciates this opportunity to provide this statement to the Senate Environment and Public Works Committee regarding chemical evaluation, risk management, and regulation. The Committee's inquiry provides an important opportunity to address the policy issues regarding chemical regulation in the United States and the chemical industry's views.

ACC is the national trade association whose member companies represent more than 90 percent of the productive capacity for basic industrial chemicals in the United States. Our members make the chemicals used in the millions of products that have made all of our lives healthier, safer, more energy efficient and more convenient. ACC's member companies share the objective of meeting consumer, scientific and industrial demands for products and processes that protect human health and the environment. Our industry's technological innovation and progress helps protect children from illness and injury, in products such as life-saving vaccines, child safety seats, and bicycle helmets, to name but a few.

Recent changes in chemicals policy in other countries and regions of the world, and at the state level, have focused attention on the adequacy of the U.S. chemical management system. ACC acknowledges the public's concern about the U.S. chemical management system, and the Council and our members are committed to supporting a regulatory program that is both scientifically sound and publicly credible. In our view, chemical regulatory programs should provide timely, scientifically-justified, efficient, effective and transparent decision-making.

ACC agrees that there are areas where the current chemical evaluation and management system in the United States can be improved and enhanced. ACC welcomes the discussion on chemicals policy, and looks forward to working with all members of the Committee to achieve our shared objective of a regulatory framework that is scientifically sound and protective of public health and the environment.

II. Chemical Regulation in the United States

The business of chemistry in the United States is subject to a myriad of chemical evaluation and risk management programs under federal, state and local laws. The Toxic Substances Control Act (TSCA) is the fundamental federal law regulating chemicals, but it is not the only federal law focused on chemical evaluation and risk management. Congress has enacted a comprehensive set of chemical regulatory statutes that affect chemical use and management in the United States, including

- Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)
- Federal Food, Drug and Cosmetics Act (FFDCA)
- Clean Air Act (CAA)
- Clean Water Act (CWA)
- Resource Conservation and Recovery Act (RCRA)
- Comprehensive Environmental Response, Compensation and Liability Act of 1980 (CERCLA)
- Emergency Planning and Community Right-to-Know Act (EPCRA)
- Occupational Safety and Health Act (OSHA)
- Hazardous Materials Transportation Act (HMTA)
- Consumer Product Safety Act (CPSA)
- Federal Hazardous Substances Act (FHSA)
- Food Quality Protection Act (FQPA)
- Chemical Facility Anti-Terrorism Standards (CFATS)
- Toxic Substances Control Act (TSCA)

A consequence of this framework is that any given chemical may be subject to multiple regulatory requirements, concurrently. For example, dispersive uses of agricultural chemicals are regulated by FIFRA and FQPA, uses of chemicals in food contact applications are regulated by the FFDCA, and uses of chemicals in consumer products are regulated under the CPSA and FHSA. This approach assures that a federal agency has appropriate regulatory authority to address the risks of chemical exposures in particular applications.

III. TSCA and Information

Information on chemicals plays a fundamental role in assessing risks. TSCA is the federal policy and regulatory tool that provides EPA with much of its information-gathering authority. EPA has used its TSCA authority to require industry to generate valuable data and information, and provide it to EPA for evaluation. The following is a brief review of the type and amount of information required of industry by EPA.

- EPA can require manufacturers and/or processors to conduct tests on specified chemical substances or mixtures in order to evaluate their human health or environmental effects. Since TSCA was enacted, **data on approximately 500 chemicals have been developed** through Section 4, through enforceable consent agreements (where EPA and companies can work together to develop a mutually agreeable test program) or under EPA's Section 5 authority.

- The Inventory Update Rule (IUR), established under EPA's TSCA Section 8 authority, requires periodic submission of production and import data for all chemicals produced or imported in quantities over a certain threshold. No other regulatory system in the world has required periodic updates on chemicals actually in commerce. **Typically over 1,000 companies have reported information to EPA under the IUR on about 9,000 chemicals in any given reporting cycle.**[1]
- Under Section 8(a), EPA has the authority to require manufacturers to maintain records and/or report on information such as categories of use, quantity manufactured or processed, by-product descriptions, health and environmental effects information, number of individuals exposed and methods of disposal. As of November 2003, EPA has issued some **33 Preliminary Assessment Information Reporting (PAIR) rules covering about 1,200 chemicals.**
- Under TSCA Section 8(d), EPA has the authority to promulgate rules to require producers, importers, and processors to submit lists and/or copies of ongoing and completed but unpublished health and safety studies. To date, **EPA has published about 50 TSCA Section 8(d) rules covering approximately 1,200 chemicals.** In response, the Agency received **more than 50,000 studies covering a broad range of health and ecological endpoints.**
- Section 8(e) of TSCA provides the EPA with a powerful information-gathering tool that serves as an early warning mechanism. EPA has received and reviewed more than **16,500 TSCA Section 8(e) notices and about 7,750 follow-up submissions.** These notices cover a wide range of chemical substances and mixtures and contain new data concerning serious adverse health effects, ecotoxicological effects and exposures.
- Under Section 5, EPA receives information from industry about new chemicals before they are manufactured. EPA has reviewed approximately **36,600 Pre-Manufacturing Notices (PMN)** since TSCA was implemented. The evaluation process involves many tools and models that can provide estimates and predictions on the potential hazards and exposures of a new chemical. This information allows EPA to develop an estimate of the potential risk of a new chemical based on its proposed use(s). **Approximately 50% of approved PMNs are subsequently brought to market, and EPA must be notified when manufacturing commences.**
- Under Section 5, **almost 3,900 PMNs** submitted to EPA were subject to some form of regulatory action, such as prescribed limitations on use or workplace practices, requirements for labeling, release and disposal restrictions, or required testing.
- TSCA Section 4(e) established the Interagency Testing Committee (ITC) to identify chemicals to which EPA should give priority consideration for collecting data and information. The ITC has reviewed more than **40,000 chemicals.** Based on ITC recommendations, **10,200 studies were submitted** to EPA.

TSCA provides EPA important authority to review and approve chemicals – regulatory authority which has been consistently exercised by the Agency.

TSCA also provides considerable flexibility to EPA in developing alternatives to the cost, burden and expense of Section 4 testing. Indeed, the Committee has heard testimony (August,

[1] Although the TSCA Inventory contains some 85,000 substances, it is important to note that the Inventory is simply a historical database. The periodic Inventory updates provide a more accurate view on the number of chemicals actually in commerce, because production status is not considered in maintaining the Inventory listing.

2006) about the value and success of the High Production Volume (HPV) Challenge program. The data and information collected in the HPV program can and are being used to decide what specific, additional toxicity tests are scientifically warranted and necessary to better understand specific organ-system hazards, and to more fully characterize the dose-response relationship. More importantly, EPA is using the HPV data to make decisions on priorities for further review under the agreement concluded last year with the Canadian and Mexican governments. All HPV data – which was always intended for screening purposes and not as a complete data set – will be assessed under the program, called the Chemical Assessment and Management Program (ChAMP) established by the Agency's Office of Pollution Prevention and Toxics. In addition, the industry has voluntarily extended the HPV chemicals to substances that newly meet the 1 million pound threshold, and by expanding reports on chemical uses and exposures through the program.

Under ChAMP, EPA will evaluate the approximately 7,000 existing chemicals produced in quantities greater than 25,000 pounds per year in the U.S by 2012. This represents the vast majority of chemicals in commerce. EPA will prioritize these chemicals for potential action based on screening-level hazard or risk assessments, based on data and information developed through the HPV and VCCEP programs, and by leveraging data and information developed by the Canadian government in its chemical prioritization program. In ACC's view, the overriding benefit of the ChAMP program is that it provides an important focus for the work of OPPT on existing chemicals in commerce. ChAMP is a logical step in chemical evaluation by EPA, and if EPA has the resources to implement it, the program will result in a basic assessment of nearly all chemicals in U.S. commerce well before any other national or regional regulatory program (including Europe's REACH program).

IV. The Integrated Risk Information System

ACC supports efforts to improve EPA's risk assessment processes to develop scientifically comprehensive and accurate risk assessments, and ACC supports transparency in the Integrated Risk Information System (IRIS). The Agency's recent improvements in the IRIS process represent an effort to foster continuous improvement practices into these important EPA activities.

Over the last 10-15 years, the IRIS assessments have required greater scientific effort and time to prepare because the science of risk assessment has advanced and the techniques and approaches applied 20 years ago are now outdated. New scientific methods must now be used in IRIS assessments. These methods include the development and application of modeling for dose extrapolation across species and routes of exposures, incorporation of biologically based modes of action, explicit evaluation of possible differential sensitivity at different life stages and use of chemical specific adjustment factors.

ACC has been concerned for some time now that the IRIS process was moving more slowly than desired. For example, many of the existing IRIS assessments are dated. We agree IRIS needs to be more effective, to both keep up with new scientific information and to reduce its backlog, and this has been ACC's long-standing perspective. We have supported efforts to

provide more resources for the IRIS program to make it more effective and scientifically up to date.

Many of the improvements in the IRIS process appear to address the findings and recommendations of the 2006 Government Accountability Office (GAO) report entitled "Human Health Risk Assessment -- EPA Has Taken Steps to Strengthen Its Process, but Improvements Needed in Planning, Data Development, and Training" (available at http://www.gao.gov/new.items/d06595.pdf). In that report the GAO recommended that 1) EPA enhance early planning of each risk assessment; 2) EPA identify and communicate data needs to the public and private research community; and 3) that the Agency support development and implementation of in-depth training for risk assessors and managers.

We believe that certain specific improvements in the IRIS process announced in April 2008 (specifically the steps of a) developing a literature search and requesting any additional information; and b) seeking comment on the qualitative assessment) will go a long way toward assuring that all the available relevant and valid scientific data will be identified early in the process so that the Agency will have this information and can incorporate it into the risk assessment in lieu of assumptions or defaults. These process improvements allow the Agency to collect scientific information on possible modes of action at the right time in the process (the qualitative assessment stage), so that these can be explored, evaluated, and if appropriate, used in the quantitative stage of the risk assessment. These improvements should contribute to more transparent and scientifically comprehensive and robust IRIS assessments that reflect the most up-to-date scientific research and knowledge.

While the risk assessments contained in the IRIS database provide important support for federal regulatory action across a number of programs, they are not the sole source of that information, and they are certainly not the sole source for EPA action under the Toxic Substances Control Act. Indeed, IRIS is not a regulatory program in and of itself, it is simply a source of information.

IV. TSCA and Voluntary Programs

In the late 1990's it became clear that publicly-available, electronically-searchable databases on chemical hazards and risks simply did not exist. In 1998, the chemical industry, working with EPA, Environmental Defense (ED) and others, developed the HPV Program to complement the Agency's testing authority under TSCA. This unprecedented voluntary initiative had the goal of making uniform health and environmental screening information on high production volume[2] (HPV) chemicals publicly available. Through the HPV Challenge Program, more than 300 sponsoring manufacturers volunteered to provide hazard-screening information on 2,222 HPV chemicals, representing 95% of the chemicals in U.S. commerce by volume. While this program emphasizes partnerships with industry, it also relies in part on EPA's exercise of its regulatory authority.

[2] High Production Volume (HPV) chemicals are those substances manufactured in or imported into the United States in amounts greater than 1 million pounds per year.

For each of the chemicals sponsored in the program,[3] industry has or will provide 17 types of information, including summarized results in four categories: physical-chemical properties, environmental fate, and potential to induce toxicity in aquatic organisms and humans. Data to be summarized for human toxicity include studies assessing acute toxicity, sub chronic toxicity, genotoxicity, and developmental and reproductive toxicity. All of the information collected under the HPV Program is important and relevant for evaluating a chemical's potential impact on human health and the environment. Additionally, test categories such as genotoxicity and acute, developmental and reproductive toxicity are specifically relevant to protecting children's health.

The HPV program and industry's work to fulfill its HPV commitments have been subject to criticism.[4] In ACC's view, those criticisms are misplaced. The fact is that the HPV program has resulted in the public availability of more information, on more chemicals, faster than any other government program anywhere in the world. Industry is proud of its record under the HPV program, and the fact that 97% of initial submissions under the program (including test plans) have been made.

In addition to the HPV program, EPA's Voluntary Children's Chemical Evaluation Program (VCCEP) pilot was developed to assess certain chemicals for potential risks to children through a series of tiered screens and tests. The VCCEP pilot is evaluating both hazard and exposure information on 20 chemicals voluntarily submitted by 35 companies and 10 consortia. The key question that the VCCEP aims to answer is whether the potential hazards, exposures, and risks to children have been adequately characterized, and if not, what additional data are necessary. Companies participating in VCCEP present a hazard assessment, exposure assessment and risk assessment on their chemical to an independent peer consultation panel, which then makes a recommendation to EPA about additional data needs under the tiered evaluation framework of the program. EPA then makes a data needs assessment about the chemical.

The VCCEP program is currently about 75% complete. ACC believes this pilot program has been very successful at affirming the viability and improved efficiencies of tiered approaches to chemical evaluation. It has also improved the practice of children's health exposure assessments and has proved the value of an independent peer consultation panel to make data needs recommendations. Although EPA data needs decisions have taken a long time, the pilot VCCEP has successfully evaluated many important chemicals, including brominated flame retardants, vinylidene chloride, benzene, and acetone. Additional detail on ACC's view of VCCEP is included in Annex A to this statement.

Importantly, the VCCEP pilot program has shown that a one-size-fits-all, single tier test battery approach to develop toxicity hazard data to address children's health questions would be

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[3] It is important to realize that industry sponsorship of chemicals in the program is voluntary. Some chemicals were not sponsored because they no longer met the 1 million pound production/import threshold to be considered high production volume chemicals; others were not sponsored because the U.S. company had a relatively small share of the market and their competition declined to join the effort. These "orphan" chemicals were expected to be the subject of test rules or consent agreements issued by EPA under its TSCA Section 4 authority.

[4] *See, e.g.*, R. Denison, High Hopes, Low Marks: A Final Report Card on the HPV Program, Environmental Defense (2007).

wasteful of laboratory animals, costly, inefficient and not nearly as informative as the risk-based approach taken under VCCEP. At the end of the day, VCCEP is providing a strong, scientific basis for deciding whether children's risks from exposure to chemicals have been adequately characterized, or whether additional information is needed to make those characterizations.[5]

In short, voluntary programs conducted under the auspices of TSCA play an important role in achieving the policy objectives set out in the Act. These programs permit companies to demonstrate their commitment to product safety, and often result in information developed in ways that are faster or less burdensome than would be the case under a regulatory mandate. More importantly, EPA retains the option to utilize its regulatory authority as it sees fit.

ACC member companies and their colleagues in the global chemical industry have also made a public commitment to enhanced transparency about chemical hazard, use and exposure information. Launched at the February 2006 United Nations International Conference on Chemicals Management, the chemical industry's Global Product Strategy (GPS) is intended to increase public and stakeholder awareness and confidence that chemicals in commerce are safely managed throughout their lifecycle. Key components of the GPS include:

- Implementing a tiered process for completing risk characterization and recommending risk management actions for chemicals in commerce.
- Making chemical health and safety information available to the public.
- Facilitating the flow of hazard and safe handling information, evaluating and mitigating risks, and addressing product challenges throughout the chemicals value chain.
- Tracking industry performance and reporting to the public.

Together, these voluntary programs illustrate how industry has taken responsible action that complements the regulatory authority already in TSCA. All of the important information generated in these voluntary programs will be used by EPA to prioritize chemicals for further evaluation, risk characterizations and risk assessment.

V. TSCA and Children's Health

The TSCA framework recognizes that understanding the connection between chemicals and children's health must be based on the concept of risk—the possibility of harm arising from exposure to a chemical or physical agent under specific conditions. When evaluating potential risk, EPA considers both toxicity and potential daily exposure over the course of a lifetime. The Agency incorporates large safety margins to assure protection of children and other sensitive groups. EPA has also developed risk assessment guidance that focuses specifically on children's health and is intended to ensure that all EPA risk assessment programs, including TSCA, protect children.

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[5] Becker et al., 2007. Tiered toxicity testing: Evaluation of toxicity-based decision triggers for human health hazard characterization. Food and Chemical Toxicology 45 (2007) 2454–2469

TSCA's Inventory Update Rule was amended in 2003 to provide EPA with more information relevant to children's health. Manufacturers of chemicals produced in amounts equal to or greater than 300,000 pounds at any facility must now report whether the chemical is used in consumer products targeted for use by children. ACC supports EPA's use of this information to prioritize its work on developing risk assessments for chemicals in commerce. EPA's insights under VCCEP will also no doubt contribute to EPA's view of what additional information is needed on priority chemicals used in children's products, and allow EPA to characterize their risks to children.

VI. TSCA and Biomonitoring

Recent advances in analytical chemistry allow scientists and others to detect trace amounts of chemicals in humans, including children. Some claim that the mere presence of a chemical in the human body means that there is a consequent risk to health. The truth is that humans are continually exposed to both naturally occurring and synthetic substances in the environment, so scientists are not surprised that with modern analytical methods, chemicals can now be detected in humans. Not only does the human body produce chemicals (chemistry indeed being essential to life), but chemicals can be absorbed through eating, breathing, drinking, and touch. According to the Centers for Disease Control and Prevention (CDC), however, simple presence of a chemical in the body does not imply a threat to health.

The National Research Council provided a comprehensive review of human biomonitoring in 2006 and concluded, among other findings, that

> *[i]n spite of its potential, tremendous challenges surround the use of biomonitoring, and our ability to generate biomonitoring data has exceeded our ability to interpret what the data mean to public health.*[6]

Furthermore, as the Centers for Disease Control and Prevention (CDC) has stated:

> *The measurement of an environmental chemical in a person's blood or urine does not by itself mean that the chemical causes disease. . . . Small amounts may be of no health consequence, whereas larger amounts may cause adverse health effects.*[7]

In California, the California Department of Public Health has communicated that, because of the limitations of human biomonitoring studies, "just because a chemical can be measured, it does not automatically mean it causes harm," and has commented that biomonitoring "may cause anxiety" and "may result in people modifying their behavior in negative ways."[8] Clearly, as the nation's leading authoritative scientific and health institutions have said, jumping to conclusions about the presence of trace concentrations in humans and purported health effects is unwarranted, both scientifically and medically.

The significance of biomonitoring levels can only be understood in a risk context. Risk is a function of both inherent toxicity and exposure. Information about the presence of chemicals in

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[6] Human Biomonitoring for Environmental Chemicals (2006), Committee on Human Biomonitoring for Environmental Toxicants, National Research Council http://books.nap.edu//catalog/11700.html#toc

[7] The *Third National Report on Human Exposure to Environmental Chemical,* CDC (2005).http://www.cdc.gov/exposurereport/pdf/thirdreport_summary.pdf

[8] California Biomonitoring Program, Overview (April 3, 2008). Diana Lee, MPH, RD, California Dept. of Public Healthhttp://www.oehha.org/multimedia/biomon/wrkshp/mats/pdf/CBPover040308.pdf

humans (exposure), when considered alone, provides an incomplete and potentially misleading picture of the risk posed by that substance. Risk assessment methods have long been used to evaluate the significance of the concentrations of chemicals in the environment, and can also be used for evaluating potential health risks of chemicals detected through human biomonitoring. It is a generally accepted principle that a chemical must exceed a certain threshold level to produce any health effect and important to understand that biomonitoring results generally show that exposure to environmental chemicals is very low, often in the parts-per-million range.

Biomonitoring information, when interpreted properly in a risk context, could prompt EPA to determine potential risks with greater scientific certainty. Based on the results of a scientifically valid biomonitoring study, EPA can use its existing authority to take appropriate action.

VII. Conclusion

The broad chemical management system in place in the United States is strong and protective of public health and the environment. Enhancements in the program can be made to address the challenges of the modern technological era, and to assure that the U.S. chemical regulatory program provides credible, scientifically-based, timely efficient and transparent decisions. As always, ACC and its members look forward to working with this Committee as chemical regulatory policy is discussed in the future.

Annex A

ACC COMMENTS ON THE
VOLUNTARY CHILDREN'S CHEMICAL EVALUATION PROGRAM

At the mid-point in the Voluntary Children's Chemical Evaluation Program (VCCEP) Pilot, the American Chemistry Council (ACC) believes the program is proceeding well. The basic structure of the pilot is sound and only minimal improvements are needed to address program efficiencies through the remainder of the pilot. Industry has lived up to its commitments under this voluntary program and the ACC believes EPA and industry should follow through on their commitments related to the pilot.

The VCCEP pilot has successfully utilized a risk-based, tiered approach to evaluate potential risk from chemical exposures and to determine what additional information or data, if any, would be needed to reduce scientific uncertainty to better characterize potential risks to children.

The VCCEP Pilot has successfully furthered EPA's and industry's understanding of how to evaluate chemicals and characterize their risks to children. Experience thus far has demonstrated that the VCCEP framework that integrates hazard and exposure information has worked well to provide extensive, reliable information related to children's health. This information will enable EPA to determine whether additional testing and/or exposure data are needed to adequately characterize potential risks to children, with a reasonable degree of scientific certainty.

ACC strongly believes that EPA should maintain the current tiered approach in VCCEP because tiered testing provides the most efficient and therefore health protective, mechanism to obtain needed information. Tiered testing provides a scientifically supportable method for assessing chemical risks. ACC objects to proposals to expedite the VCCEP pilot by collapsing Tier 2 and Tier 3 into a single Tier. While we understand the desire to complete the pilot as expeditiously as possible, proposing to change the framework in this way raises questions about the commitment to the program's original three-tiered framework. These questions in turn could create more problems for the future of VCCEP, or other voluntary programs, than the proposal aims to solve.

The innovative nature of the VCCEP evaluation approach has shown that a hazard-based "data gap" is not necessarily a "data need" with respect to characterizing children's potential risks. Devoting resources to toxicity "data gaps" irrespective of whether the specific information is actually needed (that is, data or information which is viewed as necessary to characterize children's risks with an adequate degree of scientific certainty), would be scientifically unjustifiable. The risk-based evaluative process imbedded in the VCCEP Pilot holds much promise to demonstrate how risk-based decision making can maximize risk information, and at the same time minimize laboratory animal testing, without compromising the scientific certainty needed for decision-making.

Annex A

The VCCEP Peer Consultation process has been open, transparent, timely and useful as a forum for scientists and experts from various stakeholder groups. It has been scientifically rigorous. It has been a key area of success of this program. EPA should continue to support and fund the peer consultations under the VCCEP pilot.

While there have been complaints about the timeliness of the VCCEP pilot, many of the new processes and details of this pilot required more time than industry, the peer consultation facilitator and EPA originally anticipated. Most importantly, however, because many of the chemicals that EPA selected for the pilot were relatively data rich, this has meant that industry sponsors developed data submissions that were more extensive and therefore more time consuming to prepare than originally anticipated. The result, however, has been that the sponsors' submissions moved chemical risk characterization further along and overall, saved time. The VCCEP results should be seen in the context of the time it would have taken to conduct the complex toxicity studies if EPA had issued (as originally planned) a hazard-based only test rule on children's health. Finally, ACC notes that EPA has in many instances taken longer than expected to reach its data needs decisions under the program. ACC is hopeful that as this program proceeds, performance efficiencies in all aspects of the program can be realized.

In addition to working to improve the timeliness of this program overall, ACC thinks communications about VCCEP to the public, to other EPA program offices and to other Federal and State agencies could be enhanced. In addition, EPA should make the information generated under this program more accessible. EPA should also discuss with other EPA program offices how the information it is receiving under VCCEP will be reflected in chemical risk assessments such as those in the Air and Water offices and in IRIS assessment updates.

INTEGRATIVE BIOSTRATEGIES, LLC
SCIENCE FOR DECISION-MAKING

May 2, 2008

The Honorable James M. Inhofe
Ranking Member
Committee on Environment and Public Works
415 Hart Senate Office Building
Washington, DC 20510

Dear Senator Inhofe,

First I want to thank you for the opportunity to provide testimony at the recent hearing held by the U.S. Senate Committee on Environment and Public Works (April 29, 2008), *"Oversight on EPA Toxic Chemical Policies"*. After reflecting on my testimony at the hearing, I believe it is important for me to comment on the issue raised during the hearing concerning incidence rates for various conditions, in particular cancer and changes in sperm counts in the U.S. population. During the hearing it was erroneously asserted that I had testified that cancer rates in the U.S. are decreasing. What I was actually addressing in my testimony and answers to questions was the need to assure that any statistics on disease incidence that were presented at the hearing be based on sound science and not merely statements made for impact without a basis in actual scientific data. During the hearing I was concerned and raised questions when I heard statistics being mentioned that, based on my experience, were not reflective of the actual incidences of cancer and the changes in sperm count in the U.S.

It is important to realize that data on something such as cancer incidence are complex. Statistics can be reported based on yearly incidence, incidence over time, incidence broken out by sex, age at diagnosis, mortality, etc. A scientist must consider whether any statistics collected are representative of the population of concern. The best source of such data for describing the U.S. population would be data collected in the U.S. Such an authoritative source would be the National Cancer Institute (NCI), which is a part of the National Institutes of Health, Department of Health and Human Services. Although I have not had time to do an exhaustive search of all

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the data available, there are several summaries of trends in cancer incidence over time available from NCI (*e.g.,* Ries, L.A.G. et al. (eds). SEER Cancer Statistics Review, 1975-2005, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2005/, based on November 2007 SEER data submission, posted to the SEER web site, 2008; Ries, L.A.G. et al. (eds). *Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995*, National Cancer Institute, SEER Program. NIH Pub. No. 99-4649. Bethesda, MD, 1999). Both of these documents are reliable, authoritative sources accessed by scientists when wanting to understand trends in cancer incidence in the U.S. Review of these two documents reveals that the statistics cited at the hearing on April 29th are not supported by the NCI data. In general, cancer incidence overall has remained somewhat stable over the last 30 years, with some regional, age group, and racial variations. I would refer anyone interested in citing a cancer incidence rate to those sources, with one document specific to childhood cancers.

With respect to sperm counts in the U.S., there is no one source of data that I can point to for reference. However, one authoritative source, the World Health Organization International Program for Chemical Safety (WHO/IPCS), did perform a comprehensive review of the issue of endocrine disruption (including sperm count issues) in 2002 (IPCS. 2002. *Global assessment of the state-of-the-science of endocrine disruptors*. Geneva: World Health Organization). The WHO/IPCS concluded that with respect to the hypothesis that there may be a global reduction in human semen quality (including sperm count) that might be related to environmental exposures to chemicals acting as endocrine active substances, there is not a global trend for declining semen quality that can be identified based on considering all of the available data. They found that although some studies showed declines in certain regions or cities, other studies found no evidence of such decline, suggesting there may be regional trends but not a global trend. Therefore, this authoritative source does not support the statistic quoted in the hearing related to sperm count declines.

I would be happy to provide you with further discussion of these issues if necessary. I strongly believe that science should not be used as a political tool to support one position or another, but should be used as part of a decision-making process. In this case, it is not sound science to use statistics that are not reflective of the appropriate population, or are reflective of

only one study when there is body of evidence to consider. Again thank you for the opportunity to share my views with you and the Committee.

Sincerely,

Laura M. Plunkett, Ph.D., DABT

Prostate Cancer

David F. Penson,*,† June M. Chan‡ and the Urologic Diseases in America Project

From the Departments of Urology and Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles and Departments of Epidemiology and Biostatistics, and Urology, University of California-San Francisco, San Francisco, California

Purpose: We quantified the burden of prostate cancer in the United States by identifying trends in incidence, disease presentation, survival rates and use of health care resources, and by estimating the economic impact of the disease.

Materials and Methods: The analytic methods used to generate these results were described previously.

Results: Age adjusted prostate cancer incidence rates peaked in 1992 at 237/100,000 men, decreased in 1995 and then increased at approximately 1.7% yearly through 2000, when the rate was 180/100,000. Marked stage migration and an improvement in 5-year overall survival were also noted. Age adjusted inpatient hospitalizations for prostate cancer decreased in the 1990s from 729/100,000 population in 1992 to 309/100,000 in 2001. Considerable ethnic and regional variation was noted. During the same period age adjusted radical prostatectomy rates varied from 128/100,000 men in 1994 to 108/100,000 in 2000. Surgery rates decreased in older men, while they increased in younger men. Outpatient physician office visits also varied in the 1990s with ethnic and regional variation again noted. Finally, the total medical expenditure for prostate cancer treatment was $1.3 billion in 2000, which represents a 30% increase over the total expenditure for 1994.

Conclusions: The burden of prostate cancer in the United States is considerable and it appears to have markedly increased in the prostate specific antigen era. Further research is needed to determine if we are using our limited health care resources appropriately for the diagnosis and treatment of this common malignancy.

Key Words: prostate, prostatic neoplasms, health care costs, health services research, cost and cost analysis

One of approximately every 6 American men older than 50 years is diagnosed with prostate cancer in his lifetime.[1] This astonishing statistic underscores the significance of this cancer, not only as a urological disease, but also as a general public health burden. It should be noted that the lifetime risk of prostate cancer has increased considerably in the last 15 years following the introduction of PSA testing. Although the risk of being diagnosed with prostate cancer is high, the risk of dying of the disease is much lower, in that about 1 of every 33 American men older than 50 years actually dies of prostate cancer.[2] In this respect there is truth in the clinical adage that more men die with prostate cancer than of it. While the mortality burden associated with prostate cancer is less than might be expected, the physical, psychological and economic burdens are considerable. To improve our understanding of the public health impact of this malignancy we explored the burden of prostate cancer in the United States by 1) quantifying and identifying trends in disease incidence, presentation and survival, 2) examining changing use rates of health care resources and 3) assessing the economic impact of this disease.

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† Financial relationship and/or other relationship with Pfizer, Boehringer-Ingelheim, Sanofi-Aventis and Dendreon.

‡ Financial interest and/or other relationship with Amgen.

MATERIALS AND METHODS

The analytical methods used to generate these results were described previously.[3]

RESULTS

Incidence, Presentation and Survival

Data from the National Cancer Institute SEER program were used to explore recent trends in prostate cancer incidence, disease presentation and survival in the United States. These results reflect the increasing use of serum based PSA testing, which began in the late 1980s and early 1990s. Incidence rates peaked in 1992 at 237/100,000 population (age adjusted, and all races and ages), decreased steeply until 1995 and then increased at approximately 1.7% yearly through 2000 (table 1). In 2000, 2001 and 2002 the annual age adjusted incidence rates were 180/100,000, 181/100,000 and 176/100,000 population, respectively.

Stage at diagnosis also changed dramatically in the last 20 years (table 2). During 1973 to 1979 and 1985 to 1989, 73% of prostate cancer diagnoses were localized or regional. In contrast, during 1995 to 2001, 91% of diagnoses were localized or regional. Across the same 3 intervals, the percent of patients with distant disease at diagnosis decreased from 20% to 16% to 5%, respectively.

Finally, these changes in incidence and stage at presentation were accompanied by changes in survival rates. Of white men 63% and 55% of black men diagnosed with prostate cancer in 1973 survived 5 years (table 3). For

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TABLE 1. *Incidence rates for prostate cancer by race/ethnicity and age*

Diagnosis Yr	All Males			White Males			Black Males		
	All	Younger Than 65	65 or Older	All	Younger Than 65	65 or Older	All	Younger Than 65	65 or Older
1975	94.0	13.7	649.5	92.2	13.0	639.7	141.1	27.1	929.2
1976	97.9	14.6	674.1	97.3	13.9	674.0	140.8	29.4	910.9
1977	100.4	15.0	690.8	98.5	14.3	680.6	159.2	29.2	1,057.2
1978	99.4	15.2	681.2	97.7	14.8	671.2	148.0	26.8	985.3
1979	103.4	14.9	714.9	102.3	14.6	708.1	162.0	26.4	1,100.0
1980	105.9	15.4	730.9	104.8	14.6	728.2	160.9	33.6	1,040.3
1981	108.8	16.8	745.1	107.9	16.0	743.1	161.6	34.2	1,041.9
1982	108.2	16.3	743.2	107.3	15.8	739.9	167.8	31.5	1,109.8
1983	111.6	17.1	764.2	110.7	16.6	761.6	170.9	34.1	1,116.8
1984	111.6	17.2	763.8	110.0	16.2	758.2	178.9	37.3	1,158.1
1985	115.4	17.9	790.0	114.6	17.5	785.2	169.8	31.5	1,125.8
1986	118.9	18.5	813.2	118.9	18.2	814.9	167.7	33.8	1,093.3
1987	133.5	21.5	908.1	134.3	21.1	917.4	188.9	36.2	1,244.4
1988	137.4	22.2	934.1	138.5	22.3	941.6	190.5	34.8	1,267.1
1989	145.3	24.1	982.7	146.0	24.0	989.4	191.8	37.1	1,260.8
1990	170.7	28.7	1,152.2	172.4	28.7	1,165.3	221.9	44.4	1,445.8
1991	214.5	38.8	1,429.3	216.1	39.2	1,439.1	287.9	57.2	1,882.7
1992	237.0	49.3	1,534.5	237.7	49.3	1,539.5	326.5	77.1	2,050.6
1993	209.2	50.5	1,306.1	204.0	49.0	1,275.4	342.4	93.5	2,063.3
1994	179.9	48.5	1,088.4	173.7	46.7	1,052.0	310.7	94.4	1,805.8
1995	168.5	49.8	988.7	163.4	48.0	961.3	278.5	97.3	1,631.1
1996	168.3	53.1	964.5	163.0	51.6	938.0	279.7	99.3	1,626.1
1997	172.5	55.0	984.7	168.5	53.7	961.8	278.1	96.0	1,638.8
1998	169.4	54.5	963.7	165.4	52.6	945.5	279.9	100.7	1,619.2
1999	161.3	50.5	1,016.7	176.0	58.4	988.8	285.5	109.9	1,499.2
2000	179.9	61.2	1,000.6	175.8	59.2	981.8	284.2	111.5	1,478.0
2001	180.8	63.4	992.7	178.2	61.2	986.7	280.6	111.5	1,290.7
2002	176.3	63.8	953.9	171.9	61.5	935.4	275.8	113.7	1,396.1

Rates per 100,000 age adjusted to the 2000 United States standard population (source: SEER Program [www.seer.cancer.gov] Public Use Data, 1973 to 2002, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2005, based on the November 2004 submission).

men diagnosed in 1981 survival rates increased to approximately 75% and 65% for white and black men, and for 1995 to 2000 this increased again to 100% and 96% for white and black men, respectively. Of all men essentially 100% survived 5 years or more during this more recent period if they were initially diagnosed with local/regional disease.

Health Care Resource Use

Inpatient care. The inpatient care of patients with prostate cancer often includes primary surgery (radical prostatectomy) for localized disease, management of complications of tumor or its treatment, delivery of certain forms of chemotherapy and end of life care in patients with advanced disease. Therefore, one would expect to see changes in inpatient care in the 1990s that reflected increased PSA screening and movement of care previously delivered in the inpatient setting to outpatient facilities. This is in fact what was observed.

TABLE 2. *Stage distribution by race/ethnicity for patients with prostate cancer at all ages*

	% All	% White	% Black
1975–1979:			
Localized	73	73	66
Regional	0	0	0
Distant	20	19	28
Unstaged	7	8	5
1985–1989:			
Localized	73	74	65
Regional	0	0	0
Distant	16	15	25
Unstaged	11	11	11
1995–2000:			
Localized	91	91	89
Regional	0	0	0
Distant	5	5	7
Unstaged	4	4	5

Source: SEER Program (www.seer.cancer.gov) SEER*Stat Database: Incidence–SEER 9 Regs Public Use, November 2004 Sub (1973 to 2002), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2005, based on the November 2004 submission.

Table 4 shows the total number of inpatient stays by male Medicare beneficiaries with a primary diagnosis of prostate cancer during 1992 and 2001. Overall almost 86,000 men older than 65 years were hospitalized with a primary diagnosis of prostate cancer in 1992. In contrast, fewer than 36,000 men had hospital stays in 2001. The age adjusted rate of inpatient stays decreased from 729/100,000 to 309/100,000 population between 1992 and 2001. Table 4 also indicates that the inpatient hospitalization rate was greater for black than for white American men at all time points, possibly reflecting the increasing incidence of the disease in this racial group. Trends in geographic variation in inpatient use are also interesting. Although there was a marked decrease in inpatient hospitalization in all geographic regions, the decrease between 1992 and 2001 was most striking in the West and Northeast. The reasons for this are unclear but they may reflect geographic trends in screening and treatment practices during this period.

Data from the HCUP Nationwide Inpatient Sample indicated similar trends (table 5). Hospitalization rates for prostate cancer in rural regions were less than half the rates in urban areas during 1994 to 2000. There was also geographic variation with the West having the lowest hospitalization rates in the country.

TABLE 3. *Five-year survival rates for prostate cancer by race/ethnicity, diagnosis year, stage and age*

	All Males			White Males			Black Males		
	All	Younger Than 50	50 or Older	All	Younger Than 50	50 or Older	All	Younger Than 50	50 or Older
Diagnosis yr:									
1960–1963	Not available	Not available	Not available	50.0	Not available	Not available	35.0	Not available	Not available
1970–1973	Not available	Not available	Not available	63.0	Not available	Not available	55.0	Not available	Not available
1974–1976	67.1	71.5	65.5	68.1	73.0	66.4	58.4	60.7	57.0
1977–1979	71.1	75.8	69.4	72.2	77.5	70.3	62.6	64.4	61.7
1980–1982	73.4	76.4	72.3	74.5	78.0	73.3	64.8	66.7	63.8
1983–1985	74.8	75.7	74.5	76.2	77.5	75.8	63.9	64.6	63.5
1986–1988	81.2	81.3	81.2	82.7	83.1	82.6	69.3	69.8	69.1
1989–1991	90.7	90.2	90.8	92.0	91.3	92.2	80.8	82.3	80.2
1992–1994	97.3	96.3	97.7	98.1	97.0	98.6	92.4	93.4	91.9
1995–2000	99.3*	99.1	99.7	100.0*	99.5	100.0	96.0*	98.1	95.1*
1995–2000:									
All stages	90.3	99.1	99.7	100.0	99.5	100.0	96.0		95.1
Localized/regional	100.0	100.0	100.0	100.0	100.0	100.0	100.0		100.0
Distant	33.5	30.5	34.6	32.7	30.3	33.6	29.0		28.0
Unstaged	81.4	89.3	79.4	82.8	91.3	80.9	75.5		72.4
Diagnosis age:									
Younger than 45	91.7	Not available	Not available	91.3	Not available	Not available	95.4	Not available	Not available
45–54	97.2	Not available	Not available	97.5	Not available	Not available	96.8	Not available	Not available
55–64	99.7	Not available	Not available	100.0	Not available	Not available	98.4	Not available	Not available
65–74	100.0	Not available	Not available	100.0	Not available	Not available	98.1	Not available	Not available
75 or Older	94.8	Not available	Not available	98.5	Not available	Not available	87.5	Not available	Not available
Younger than 65	90.1	Not available	Not available	99.5	Not available	Not available	98.1	Not available	Not available
65 or Older	99.7	Not available	Not available	100.0	Not available	Not available	95.1	Not available	Not available

Rates for 1960 to 1973 based on End Results data from a series of hospital registries and 1 population based registry, and rates for 1974 to 2000 from SEER 9 areas, based on data from population based registries in Connecticut, Puerto Rico, Utah, Iowa, Hawaii, Atlanto, Detroit, Seattle-Puget Sound and San Francisco-Oakland, and based on followup of patients into 2001 (survival rate SE of 5% to 10%) (source: SEER Program [www.seer.cancer.gov] SEER*Stat Database: Incidence–SEER 9 Regs Public Use, submission November 2004 Sub (1973 to 2002), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2005, based on the November 2004 submission).

* Statistically significant difference vs 1974 to 1976 ($p < 0.05$).

It is likely that changes in inpatient prostate cancer care were related at least in part to radical prostatectomy use rates. To explore this hypothesis HCUP data were used to examine trends in radical prostatectomy. Radical prostatectomy rates were relatively stable in 1994 and 1996 (128/100,000 and 127/100,000 men older than 40 years, respectively) but rates decreased in 1998 to 99/100,000 and then increased again in 2000 to 108/100,000 (table 6). Importantly when prostatectomy rates were stratified by age, rates decreased consistently in patients older than 65 years, while there were consistent increases in the rates for patients 40 to 54 years old. Briefly, there were significant changes in the use of radical prostatectomy in the last 15 years with the overall rate of use decreasing in older men but increasing in younger men. This likely influenced trends in inpatient prostate cancer care.

Outpatient care. Although the inpatient component of care is important, most prostate cancer survivors receive a significant portion of their care as outpatients. We focused on a single aspect of outpatient care, that is physician office visits. NAMCS data documented that the average annual age adjusted rate of physician office visits for prostate cancer in 1992 to 2000 was 5,001/100,000 American males older than 40 years (table 7). The rate was 5,449/100,000 in 1992 and it decreased to a low of 3,870/100,000 in 1998. It then increased to 5,828/100,000 in 2000. The exact reasons for these shifts are unclear. In this period men 75 to 84 years old had the highest rate of office visits compared with that in men 65 to 74 and 40 to 64 years old (112,069/100,000 vs 54,445/100,000 and 5,930/100,000, respectively). This may be explained by the fact that older patients are least likely to undergo aggressive therapy for localized disease and most likely to elect conservative management. Therefore, they may be seen more often by their providers and may require more outpatient care.

Data from the Medicare sample did not show the same decrease between 1992 and 1998. Rather, they indicated that the rate of physician office visits increased from 1992 to 1995 and remained relatively stable after that, reflecting changes in the age adjusted incidence rate of prostate cancer (table 8). Differences between NAMCS and Medicare data may be explained by the fact that Medicare patients were older and likely had somewhat different patterns of care than the younger patients in the NAMCS sample. There was considerable geographic variation in physician office visit rates in the NAMCS and Medicare samples, although the differences were not consistent between the 2 data sets. It is likely that physician office visits were related to patterns of care in primary treatment choice. The relation of primary treatment to geographic region and patient age would explain the differing patterns of geographic variation between the 2 samples.

Economic Impact

Medical expenditures for prostate cancer treatment in the United States totaled $1.3 billion in 2000, almost 30% more than in 1994 (table 9). The growth in spending occurred despite a decrease in hospitalization costs as treatment shifted from inpatient to outpatient settings. Spending on treatment provided in physician offices more than tripled between 1994 and 2000, while expenditures for ambulatory surgery more than doubled during this period. By 2000

TABLE 4. *Inpatient hospital stays by male Medicare beneficiaries with prostate cancer listed as primary diagnosis*

	1992			1995			1998			2001		
	Count	Rate (95% CI)	Age Adjusted Rate	Count	Rate (95% CI)	Age Adjusted Rate	Count	Rate (95% CI)	Age Adjusted Rate	Count	Rate (95% CI)	Age Adjusted Rate
Total all ages	87,540	598 (570–605)		50,620	333 (320–346)		38,540	268 (256–280)		37,840	245 (234–256)	
Total younger than 65	1,720	55 (43–67)		1,740	51 (40–61)		1,460	42 (33–52)		1,960	49 (39–59)	
Total 65 or older	85,820	729 (707–751)	729	48,880	415 (399–432)	410	37,080	339 (323–354)	337	35,880	310 (295–324)	309
Age:												
65–69	27,620	679 (643–714)		17,260	448 (418–478)		12,680	376 (346–405)		12,340	349 (321–376)	
70–74	27,720	853 (808–897)		15,240	467 (425–489)		11,500	377 (346–408)		10,620	342 (313–371)	
75–79	16,580	732 (683–782)		7,360	324 (291–358)		5,700	250 (221–279)		5,820	237 (210–264)	
80–84	8,720	666 (603–728)		5,300	381 (336–427)		3,800	276 (237–315)		3,540	237 (202–271)	
85–89	3,780	634 (544–724)		2,340	367 (301–434)		2,580	397 (328–465)		2,500	346 (285–406)	
90–94	1,200	592 (442–742)		1,060	501 (357–636)		920	428 (304–551)		1,040	449 (327–571)	
95–97	160	396 (121–671)		200	531 (202–859)		160	405 (158–750)		140	364 (94–635)	
98 or Older	40	105 (0.0–250)		120	271 (54–488)		20	42 (0.0–123)		80	147 (3.7–291)	
Race/ethnicity:												
White	74,280	591 (572–610)	592	42,800	329 (315–343)	330	32,200	263 (250–276)	263	31,400	240 (228–252)	240
Black	8,600	674 (611–737)	646	5,860	423 (375–472)	412	4,580	366 (326–411)	355	4,580	319 (276–360)	315
Asian	Not available	Not available	Not available	100	137 (16–256)	137	160	117 (36–198)	131	140	68 (18–119)	68
Hispanic	Not available	Not available	Not available	560	282 (178–386)	282	740	220 (150–291)	215	640	170 (111–229)	160
North American native	Not available	Not available	Not available	40	199 (0.0–472)	298	60	216 (0.0–458)	143	100	300 (36–565)	240
Region:												
Midwest	20,840	562 (528–596)	566	11,700	304 (278–328)	300	10,220	276 (252–300)	279	9,620	253 (231–276)	256
Northeast	18,620	587 (550–625)	573	11,760	370 (340–400)	360	7,420	267 (240–294)	270	6,720	230 (206–255)	221
South	32,260	616 (586–646)	616	19,360	363 (337–375)	357	14,960	279 (259–299)	277	15,180	261 (243–280)	262
West	14,720	609 (566–653)	622	7,200	310 (276–343)	322	5,700	256 (225–284)	251	6,660	229 (202–255)	231

Unweighted counts multiplied by 20 to arrive at values, rate per 100,000 male Medicare beneficiaries in the same demographic stratum, age adjusted rates adjusted to the 2000 United States Census and individuals of other races, unknown race and ethnicity, and other region included in the total (counts less than 600 should be interpreted with caution) (source: Centers for Medicare and Medicaid Services, Medicare Provider Analysis and Review Files, 1992, 1995, 1998 and 2001).

TABLE 5. *Inpatient hospital stays for prostate cancer as primary diagnosis for 1994 to 2000 (merged)*

	1994–2000		
	Count	4-Yr Rate (95% CI)	Av Annualized Rate/yr
Totals	407,042	815 (780–851)	204
Age:			
40–44	1,651	16 (13–19)	4.0
45–54	33,749	211 (189–234)	53
55–64	118,051	1,143 (1,064–1,223)	286
65–74	161,183	2,006 (1,929–2,084)	502
75–84	69,400	1,598 (1,544–1,652)	400
85 or Older	23,009	2,441 (2,338–2,544)	610
Race/ethnicity:			
White	260,321	651 (614–687)	163
Black	37,954	821 (769–872)	205
Hispanic	14,584	412 (368–456)	103
Region:			
Midwest	96,752	827 (766–887)	207
Northeast	89,190	887 (817–956)	222
South	148,779	851 (772–929)	213
West	72,322	677 (626–728)	169
MSA:			
Urban	352,310	939 (893–985)	235
Rural	53,269	429 (397–461)	107

Rate per 100,000 based on 1994, 1996, 1998 and 2000 population estimates from CPS, CPS Utilities, Unicon Research Corp. for relevant demographic categories of adult male civilian noninstitutionalized population 40 years or older in the United States with individuals of other races and with missing or unavailable race and ethnicity, and missing MSA included in the total (counts may not sum to total due to rounding) (source: HCUP Nationwide Inpatient Sample, 1994, 1996, 1998 and 2000).

inpatient expenditures accounted for 48% of total spending on prostate cancer, down from 69% in 1994.

Because prostate cancer primarily affects older males, more than two-thirds of all spending for the condition was borne by the Medicare program. Medicare reimbursements for prostate cancer totaled $846 million in 1992 and $927 million in 2001 (table 10). Medicare spending among beneficiaries younger than 65 years increased from $16 million in 1992 to more than $38 million in 2001, largely due to increased screening.

Individual level expenditures were estimated using risk adjusted regression models controlling for age, work status, geographic location and health plan characteristics. For males 40 to 64 years old with employer provided insurance average annual expenditures for prostate cancer totaled $11,445 compared with $4,426 for similar men without the condition (table 11). This suggests that the annual incremental costs associated with prostate cancer exceeded $7,000 per individual. Average spending was higher for men 40 to 54 years and in the West, although regional variation was modest.

DISCUSSION

Prostate cancer is the most common urological malignancy and the most common solid cancer found in American men. Disease incidence, stage at presentation and 5-year survival rates changed dramatically in the last 20 years following the introduction of PSA testing, which resulted in widespread screening for this cancer throughout the United States and Western Europe. Our data demonstrate that short-term survival rates improved in the PSA era. Others documented that overall long-term mortality[4] and disease specific mortality rates[5] also appeared to be decreasing in the PSA era. It was speculated that these decreases reflect the beneficial effects of early diagnosis with PSA screening or improved treatments. However, it was also noted that decreases in mortality may be attributable to other causes, such as earlier and widespread use of androgen deprivation therapy. Specifically Lu-Yao et al compared prostate cancer specific mortality between 2 population based cohorts of men with prostate cancer from King County, Wnshington and Connecticut.[6] Although PSA use rates and treatment patterns differed widely between the 2 populations, prostate cancer mortality was comparable, implying that more intensive screening was not associated with the decrease in mortality. Formal, randomized, clinical trial data on PSA screening in the general population are anticipated from the European Randomized Screening for Prostate Cancer Trial, and the Prostate, Lung, Colorectal and Ovary cancer trial within the next several years. These data should provide a better understanding of the value of prostate cancer screening for decreasing mortality. However, in the meantime prostate cancer screening has been embraced by the clinical community and the general population, and it likely will continue to be widely used.

Patterns of care also changed tremendously in the last 20 years. Some of these changes were directly related to the introduction of PSA testing, while others reflect improved understanding of prostate cancer by clinicians and researchers. In particular older men with shorter life expectancies are on average receiving less aggressive therapy than in the past, reflecting the clinician realization that older men are at decreased risk for prostate cancer mortality due to competing comorbid diseases. For example, Bubolz et al reviewed the Medicare part A data set for 1993 to 1997 and documented that external beam radiotherapy rates were relatively stable for all patients except those older than 75 years.[7] In older patients external beam radiotherapy use decreased, reflecting the general realization by providers that many of these patients did not require any treatment, given their relatively short life expectancy and comorbid conditions.

In contrast, our data and those of others[8] showed that more men are being diagnosed at younger ages and with earlier stage disease. Therefore, they are undergoing more aggressive therapies for the condition. Surgical rates have consistently increased in these younger patients. There is considerable racial and geographic variation in treatment use, although this is probably the result of clinical uncertainty as to which treatment is best for men with localized prostate cancer. Additional level I clinical trial data are desperately needed to identify which patients are best served by which therapies. Although there is a single randomized clinical trial documenting that surgery is superior to active surveillance for overall survival when patients are followed for a long enough period,[9] there are no adequately sized clinical trials comparing active therapies to each other in terms of survival. Until these studies are completed there will be continued ethnic and regional variations in practice patterns and the quality of prostate cancer care will be suboptimal.

Finally, data from the current analyses document that there is a tremendous economic burden associated with the diagnosis and treatment of prostate cancer in the United States. It should be noted that the dollar figures presented still do not capture all of the costs of this common disease.

TABLE 6. *Radical prostatectomy in men hospitalized for primary diagnosis of prostate cancer*

	1994			1996			1998			2000		
	Count	Rate/100,000 Population (95% CI)	Rate/100,000 Hospitalizations for Primary Prostate Ca Diagnosis (95% CI)	Count	Rate/100,000 Population (95% CI)	Rate/100,000 Hospitalizations for Primary Prostate Ca Diagnosis (95% CI)	Count	Rate/100,000 Population (95% CI)	Rate/100,000 Hospitalizations for Primary Prostate Ca Diagnosis (95% CI)	Count	Rate/100,000 Population (95% CI)
Totals	58,254	128 (128–128)	50,553 (50,440–50,666)	81,952	127 (126–127)	57,851 (57,710–57,992)	60,943	99 (99–99)	57,861 (57,744–57,978)	58,191	106 (105–106)
Age:*											
40–54	5,467	23 (23–24)	4,744 (4,721–4,768)	7,573	29 (29–30)	7,072 (7,039–7,104)	7,439	27 (27–27)	8,449 (8,416–8,483)	10,198	36 (35–35)
55–64	22,683	236 (235–237)	19,684 (19,621–19,749)	25,288	254 (254–255)	23,514 (23,452–23,576)	21,267	201 (200–201)	24,156 (24,090–24,219)	26,125	234 (234–235)
65–74	23,444	361 (360–362)	24,664 (24,612–24,716)	27,961	341 (340–342)	26,017 (25,958–26,076)	21,161	263 (262–264)	24,104 (24,054–24,155)	20,315	253 (252–253)
75–84	1,649	43 (42–45)	1,411 (1,395–1,427)	1,220	29 (28–30)	1,139 (1,095–1,183)	1,076	24 (23–25)	1,222 (1,176–1,270)	1,025	21 (20–22)
Race/ethnicity:			34,196 (34,103–34,288)								
White	39,405	107 (106–107)	3,650 (3,640–3,660)	42,773	106 (106–109)	39,942 (39,829–40,056)	32,845	80 (80–81)	37,306 (37,211–37,399)	35,009	82 (82–82)
Black	4,218	102 (102–103)	1,327 (1,313–1,342)	5,188	116 (116–116)	4,846 (4,832–4,857)	4,307	90 (89–90)	4,892 (4,859–4,926)	4,784	94 (93–94)
Hispanic	1,529	50 (50–51)		1,626	50 (49–50)	1,518 (1,503–1,533)	2,117	55 (55–56)	2,404 (2,383–2,426)	2,210	55 (54–55)
Region:			8,069 (8,014–8,104)								
Northeast	9,287	96 (95–96)	12,294 (12,233–12,357)	12,237	124 (124–125)	11,427 (11,384–11,470)	10,594	108 (107–108)	12,497 (12,427–12,548)	12,924	128 (128–134)
Midwest	14,167	133 (132–134)	20,401 (20,317–20,485)	16,212	139 (138–139)	15,139 (15,092–15,187)	11,749	99 (98–99)	13,344 (13,286–13,403)	13,853	110 (110–111)
South	23,569	153 (152–153)	9,738 (9,706–9,831)	23,450	137 (136–137)	21,598 (21,795–22,022)	17,997	95 (95–95)	19,657 (19,582–19,731)	20,758	108 (108–108)
West	11,231	116 (115–116)		10,052	98 (98–99)	9,687 (9,317–9,466)	10,603	98 (97–98)	12,272 (12,207–12,406)	10,657	99 (99–99)
MSA:											
Rural	6,255	50 (50–51)	5,428 (5,401–5,456)	5,898	50 (49–50)	5,508 (5,455–5,559)	6,183	42 (42–42)	5,887 (5,855–5,919)	5,888	45 (45–46)
Urban	51,788	157 (156–157)	44,324 (44,814–45,034)	55,863	151 (151–151)	52,184 (52,054–52,314)	45,599	117 (116–117)	51,791 (51,676–51,904)	52,345	128 (127–128)

Rate per 100,000 based on 1994 to 2000 population estimates from CPS, CPS Utilities, Unicon Research Corp. for relevant demographic categories of adult male civilian noninstitutionalized population 40 years or older in the United States, rate per 100,000 male 40 years or older visits with radical prostatectomy performed based on estimated number of visits for prostate cancer in HCUP National Inpatient Sample, 1994 to 2000 and including one of four races, and with missing or unavailable race and ethnicity, and missing MSA included in the total (counts may not sum to total due to rounding) (source: HCUP Nationwide Inpatient Sample, 1994, 1996, 1998, and 2000).

* Values for ages 35 years or older do not meet reliability or precision standard.

TABLE 7. *Physician office visits for prostate cancer as primary diagnosis*

	1992–2000				1992			1994			
	Count	Rate	Av Annualized Rate/Yr	Age Adjusted Rate	Count	Rate	Age Adjusted Rate	Count	Rate	Age Adjusted Rate	Count
Totals	12,236,564	25,004 (22,610–27,198)	5,001	25,034	2,450,034	5,449 (4,410–6,487)	5,449	2,234,596	4,910 (4,112–5,709)	4,910	2,420,055
Age:											
40–64	2,118,240	5,930 (4,647–7,212)	1,186		*	*		301,211	914 (515–1,314)		*
65–74	4,399,702	54,445 (48,664–60,226)	10,889		832,868	10,070 (8,717–13,423)		783,398	9,946 (7,212–12,681)		964,667
75–84	4,739,092	112,069 (95,718–128,421)	22,414		1,007,893	26,753 (19,874–34,632)		993,754	26,206 (19,613–32,796)		936,418
85 or Older	979,530	108,031 (79,920–136,242)	21,606		*	*		*	*		*
Race/ethnicity:											
White	10,498,163	26,564 (24,119–29,170)	5,329	25,313	2,217,258	5,998 (4,799–7,197)	5,730	1,893,654	5,120 (4,222–6,018)	4,881	2,159,471
Other	1,738,401	18,227 (14,091–22,452)	3,645	23,366	*	*	*	340,932	4,000 (2,270–5,730)	5,109	*
Region:											
Midwest	2,906,831	25,282 (20,840–29,683)	5,052	25,086	*	*	*	535,052	5,190 (3,971–7,209)	5,649	520,291
Northeast	3,718,177	37,425 (31,382–43,468)	7,465	36,556	817,237	8,649 (6,016–11,282)	8,360	695,338	7,184 (4,685–9,643)	7,018	665,572
South	3,187,693	18,669 (15,599–21,740)	3,734	18,435	647,909	4,207 (2,690–5,723)	4,139	595,211	3,868 (2,760–4,976)	3,888	670,950
West	2,423,763	23,256 (18,398–28,114)	4,651	24,738	614,662	6,544 (3,718–9,369)	6,885	348,985	3,573 (2,303–4,843)	3,687	563,242
MSA:											
MSA	10,498,173	29,760 (25,598–31,622)	5,752	29,935	2,166,249	6,651 (5,305–7,997)	6,922	1,839,675	5,559 (4,557–6,561)	5,781	1,965,145
NonMSA	1,738,391	13,978 (11,014–16,943)	2,796	13,936	*	*	*	395,911	3,184 (1,985–4,384)	2,943	*

Rate per 100,000 based on 1992, 1994, 1996, 1998 and 2000 population estimates from CPS, CPS Utilities, Union Research Corp. for relevant demographic categories of male civilian noninstitutionalized population 40 years or older in the United States, age-adjusted (grouped years adjusted to the United States Census derived age distribution of the mid point of years, individual years age adjusted to the United States Census derived age distribution of the year under analysis and individuals with missing or unavailable race and ethnicity, and missing MSA included in the total (counts may not sum to total due to rounding) (source: NAMCS, 1992, 1994, 1996, 1998 and 2000).

* Values do not meet reliability or precision standard.

TABLE 8. *Physician office visits by male Medicare beneficiaries with prostate cancer as primary diagnosis*

	1992			1995			1998			2001		
	Count	Rate (95% CI)	Age Adjusted Rate	Count	Rate (95% CI)	Age Adjusted Rate	Count	Rate (95% CI)	Age Adjusted Rate	Count	Rate (95% CI)
Total all ages	1,660,000	10,738 (10,668–10,808)		2,370,000	15,543 (15,462–15,625)		2,240,000	15,472 (15,388–15,555)		2,280,000	14,755 (14,705–14,804)
Total younger than 65	19,220	615 (577–654)		36,040	1,046 (996–1,094)		42,720	1,243 (1,191–1,296)		46,520	1,250 (1,180–1,320)
Total 65 or older	1,580,000	13,424 (13,337–13,511)	14,389	2,330,000	19,786 (19,684–19,887)	20,978	2,200,000	18,900 (18,795–20,005)	20,561	2,250,000	19,227 (19,126–19,328)
Age:											
65–69	295,900	7,267 (7,155–7,380)		398,440	10,344 (10,208–10,480)		363,940	10,778 (10,630–10,926)		368,740	10,421 (10,278–10,563)
70–74	422,160	12,984 (12,820–13,147)		614,140	18,417 (18,231–18,603)		573,240	18,792 (18,596–18,988)		545,520	17,721 (17,531–17,912)
75–79	419,420	18,529 (18,303–18,755)		606,600	26,741 (26,494–26,999)		594,320	26,025 (25,771–26,280)		598,926	24,414 (24,174–24,655)
80–84	294,660	21,728 (21,413–22,044)		444,260	31,975 (31,629–32,322)		414,980	30,115 (29,773–30,458)		433,669	28,977 (28,652–29,302)
85–89	124,620	20,902 (20,440–21,383)		205,980	32,339 (31,825–32,853)		189,160	29,687 (29,190–30,183)		220,626	30,494 (30,020–30,969)
90–94	29,480	14,555 (13,868–15,242)		52,520	24,846 (24,022–25,670)		50,180	23,327 (22,527–24,126)		57,380	24,785 (23,979–25,591)
95–97	3,280	8,119 (6,928–9,309)		6,280	18,868 (14,976–18,340)		6,500	13,896 (12,372–15,419)		6,060	15,773 (14,144–17,402)
98 or Older	880	2,318 (1,641–2,995)		1,420	3,208 (2,472–3,939)		2,060	4,181 (3,378–4,983)		2,206	4,065 (3,312–4,797)
Race/ethnicity:											
White	1,390,000	11,047 (10,969–11,124)	10,991	2,070,000	15,961 (15,872–16,050)	15,882	1,950,000	15,951 (15,859–16,042)	15,965	1,960,000	15,008 (14,919–15,095)
Black	127,840	10,019 (9,788–10,252)	10,039	219,620	15,864 (15,588–16,133)	16,553	205,760	15,491 (15,216–15,765)	15,107	217,480	14,818 (14,541–15,076)
Asian	Not available	Not available	Not available	8,980	12,322 (11,254–13,389)	11,650	14,340	10,694 (10,157–11,231)	10,704	15,020	7,330 (6,825–7,834)
Hispanic	Not available	Not available	Not available	16,360	8,250 (7,709–8,792)	8,814	39,900	11,893 (11,403–12,383)	12,167	41,960	11,167 (10,717–11,618)
North American native	Not available	Not available	Not available	640	3,181 (2,697–4,264)	2,983	1,200	4,292 (3,230–5,354)	4,220	1,360	4,084 (3,132–5,036)
Region:											
Midwest	362,260	9,766 (9,631–9,902)	9,826	531,420	13,766 (13,632–13,940)	13,942	505,180	13,661 (13,504–13,817)	13,708	495,440	13,044 (12,893–13,195)
Northeast	344,580	10,866 (10,713–11,019)	10,909	573,600	18,035 (17,846–18,224)	17,937	507,460	15,259 (15,056–15,462)	15,050	504,160	17,253 (17,060–17,447)
South	603,420	11,520 (11,396–11,642)	11,465	875,680	15,962 (15,825–16,099)	16,014	861,120	16,044 (15,905–16,183)	16,292	894,900	15,410 (15,279–15,541)
West	272,220	11,270 (11,091–11,448)	11,213	356,680	15,381 (15,173–15,589)	15,111	330,420	14,775 (14,567–14,983)	14,389	344,760	13,930 (13,737–14,123)

Unweighted counts multiplied by 20 to arrive at values; rate per 100,000 male Medicare beneficiaries in the same demographic stratum, age-adjusted rate adjusted to the 2000 United States Census and individuals of other races, unknown race and ethnicity, and other region included in the total (counts less than 600 should be interpreted with caution) (source: Centers for Medicare and Medicaid Services, 5% Carrier and Outpatient Files, 1992, 1995, 1998 and 2001).

TABLE 9. *Expenditures for prostate cancer by service site*

	$ Expenditure (% total)
1994:	
Hospital outpt	129,108,028 (12.9)
Physician office	97,839,385 (9.8)
Ambulatory surgery	76,645,818 (7.5)
Emergency room	9,590,867 (1.0)
Inpt	689,630,760 (68.9)
Total	1,002,814,857
1996:	
Hospital outpt	62,968,055 (6.5)
Physician office	115,394,094 (12.0)
Ambulatory surgery	77,341,725 (8.0)
Emergency room	10,444,787 (1.1)
Inpt	697,677,985 (72.4)
Total	963,846,646
1998:	
Hospitol outpt	112,133,820 (11.8)
Physician office	143,409,456 (15.1)
Ambulatory surgery	141,018,192 (14.9)
Emergency room	13,811,416 (1.5)
Inpt	537,794,704 (56.7)
Total	948,167,588
2000:	
Hospital outpt	174,484,751 (13.5)
Physician office	305,584,466 (23.6)
Ambulatory surgery	179,080,421 (13.8)
Emergency room	15,553,104 (1.2)
Inpt	621,098,169 (47.9)
Total	1,295,800,912

Source: NAMCS, National Hospital and Ambulatory Medical Care Survey, HCUP and Medical Expenditure Panel Survey, 1994, 1996, 1998 and 2000.

For example, there may be additional indirect costs due to premature retirement and lost productivity that were not captured in the Urologic Diseases in America data sets.

Max et al estimated the indirect costs of prostate cancer in California by estimating patient lost (lifetime) earnings discounted at a 3% annual rate.[10] They estimated that the indirect costs due to premature mortality totaled $160 million, equal to the direct medical costs of treating the condition. Bradley et al queried a population based cohort of prostate cancer survivors and age matched controls, and found that men with prostate cancer were 10% less likely to be working 6 months after a prostate cancer diagnosis than those without the disease.[11] More importantly at 1 year 26% of prostate cancer survivors who returned to work reported that the disease interfered with their ability to function on the job.

Finally, the reader is reminded that Medicare expenditures for medical androgen suppression therapy amounted to $478 million in 1994, representing 34% of the total Medicare expenditure for prostate cancer.[12] These values are likely to have increased in the last decade since the use of drug therapy has increased rapidly.[13,14] Medicare recently decreased the reimbursement rates for outpatient hormonal ablation therapy, which will likely decrease the overall economic burden of this treatment in the future. Nevertheless, these treatments still contribute greatly to the overall cost of prostate cancer in the United States and they may represent an area for which cost savings could be generated.

CONCLUSIONS

Prostate cancer is a significant public health problem in the United States. This tumor remains the most common solid tumor in American men and the second leading cause of cancer death. While the debate regarding prostate cancer screening continues, there is no argument that the incidence of the disease has increased in the PSA era. Not surprisingly there has been a stage migration and a decrease in short-term mortality rates. Whether this is due to a true beneficial effect of screening, or to lead or lag time bias still remains to be seen.

The introduction of PSA screening has had a major impact on health care use rates in prostate cancer. Use of inpatient care decreased in the 1990s, while radical prostatectomy rates decreased in older patients and increased in younger ones. Outpatient health care use increased as the overall number of men living with prostate cancer also increased, and many of the elements of prostate cancer care were shifted to the outpatient setting. There is significant regional and ethnic variation in patterns of health care use, reflecting clinical uncertainty regarding the optimal treatment for this condition. Only through well designed, randomized clinical trials will we be able to eliminate this variation and determine the optimal care for men newly diagnosed with prostate cancer.

TABLE 10. *Medicare beneficiary expenditures for prostate cancer treatment*

	$ Expenditures (% total)			
Service Type	1992	1995	1998	2001
65 or Older:				
Hospital outpatient	199,884,080 (24.1)	185,917,800 (28.4)	215,481,000 (30.0)	250,870,360 (28.2)
Physician office	74,274,100 (9.0)	107,163,440 (16.4)	158,207,040 (22.0)	227,776,200 (25.6)
Ambulatory surgery	53,091,600 (6.4)	53,352,000 (8.2)	116,847,360 (16.2)	160,356,000 (18.0)
Emergency room	2,455,000 (0.3)	2,665,680 (0.4)	1,869,840 (0.3)	2,218,220 (0.2)
Inpatient	500,158,960 (60.3)	305,255,600 (46.6)	226,821,840 (31.5)	247,542,400 (27.9)
Totals	829,863,740	654,954,520	719,227,080	888,763,180
Younger than 65:				
Hospital outpatient	2,522,800 (15.6)	5,149,360 (27.7)	6,003,440 (26.6)	6,998,500 (23.3)
Physician office	922,560 (5.7)	1,910,120 (10.3)	3,118,560 (13.8)	4,447,900 (11.5)
Ambulatory surgery	805,200 (5.0)	0 (0.0)	3,526,400 (15.6)	8,342,880 (21.6)
Emergency room	— (0.0)	— (0.0)	— (0.0)	— (0.0)
Inpatient	11,936,800 (73.7)	11,558,820 (62.1)	9,952,820 (44.0)	16,872,060 (43.6)
Totals	16,187,360	18,618,300	22,601,220	38,661,340

Source: Centers for Medicare and Medicaid Services, 1992, 1995, 1998 and 2001.

TABLE 11. *Estimated annual expenditures for privately insured employees with and without prostate cancer medical claim in 2002*

	$ Annual Expenditures/Pt Ages 50–64 Without Prostate Ca (203,181 men)			$ Annual Expenditures/Pt Ages 50–64 With Prostate Ca (3,135 men)		
	Medical	Prescription Drugs	Totals	Medical	Prescription Drugs	Totals
All	3,182	1,244	4,426	9,551	1,894	11,445
Age:						
50–54	3,302	1,306	4,608	8,108	1,797	9,905
55–59	3,460	1,291	4,751	6,997	1,768	8,765
60–64	3,302	1,159	4,461	6,181	1,859	8,040
Region:						
Midwest	2,996	1,232	4,228	8,989	1,888	10,877
Northeast	3,110	1,332	4,442	9,331	2,033	11,364
South	3,322	1,176	4,497	9,965	1,782	11,747
West	3,439	1,238	4,677	10,317	1,908	12,225

Primary beneficiaries 40 to 64 years old with employer provided insurance who were continuously enrolled in 2002, estimated annual expenditures were derived from multivariate models controlled for age, gender, work status (active/retired), median household income based on zip code, urban/rural residence, medical and drug plan characteristics (managed care, deductible and co-insurance/co-payments) and binary indicators for 28 chronic disease conditions with predicted expenditures for males 40 to 49 years old are omitted due to small sample size (source: Ingenix, 2002).

Abbreviations and Acronyms

CPS = Current Population Survey
DPPS = Division of Prevention and Population Sciences
HCUP = Health Care Cost and Utilization Project
MSA = metropolitan statistical area
NAMCS = National Ambulatory Medical Care Survey
PSA = prostate specific antigen
SEER = Surveillance, Epidemiology and End Results Program

REFERENCES

1. Merrill RM, Weed DL and Feuer EJ: The lifetime risk of developing prostate cancer in white and black men. Cancer Epidemiol Biomarkers Prev 1997; 6: 763.
2. Merrill RM and Stephenson RA: Trends in mortality rates in patients with prostate cancer during the era of prostate specific antigen screening. J Urol 2000; 163: 503.
3. Litwin MS, Saigal CS, Yano EM, Avila C, Geschwind SA, Hanley JM et al: Urologic Diseases in America Project: analytical methods and principal findings. J Urol 2005; 173: 933.
4. Chan JM, Jou RM and Carroll PR: The relative impact and future burden of prostate cancer in the United States. J Urol 2004; 172: S13.
5. Bartsch G, Horninger W, Klocker H, Reissigl A, Oberaigner W, Schonitzer D et al: Prostate cancer mortality after introduction of prostate-specific antigen mass screening in the Federal State of Tyrol, Austria. Urology 2001; 58: 417.
6. Lu-Yao G, Albertsen PC, Stanford JL, Stukel TA, Walker-Corkery ES and Barry MJ: Natural experiment examining impact of aggressive screening and treatment on prostate cancer mortality in two fixed cohorts from Seattle area and Connecticut. BMJ 2002; 325: 740.
7. Bubolz T, Wasson JH, Lu-Yao G and Barry MJ: Treatments for prostate cancer in older men: 1984–1997. Urology 2001; 58: 977.
8. Ellison LM, Heaney JA and Birkmeyer JD: Trends in the use of radical prostatectomy for treatment of prostate cancer. Eff Clin Pract 1999; 2: 228.
9. Bill-Axelson A, Holmberg L, Ruutu M, Haggman M, Andersson SO, Bratell S et al: Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med 2005; 352: 1977.
10. Max W, Rice DP, Sung HY, Michel M, Breuer W and Zhang X: The economic burden of prostate cancer, California, 1998. Cancer 2002; 94: 2906.
11. Bradley CJ, Neumark D, Luo Z, Bednarek H and Schenk M: Employment outcomes of men treated for prostate cancer. J Natl Cancer Inst 2005; 97: 958.
12. Cancer Facts and Figures, 2005. Atlanta: American Cancer Society 2005.
13. Cooperberg MR, Grossfeld GD, Lubeck DP and Carroll PR: National practice patterns and time trends in androgen ablation for localized prostate cancer. J Natl Cancer Inst 2003; 95: 981.
14. Zeliadt SB, Potosky AL, Etzioni R, Ramsey DS and Penson DF: Racial disparity in primary and adjuvant treatment for nonmetastatic prostate cancer: SEER-Medicare trends 1991 to 1999. Urology 2004; 64: 1171.

O-1. BACKGROUND AND DATA SOURCES

There are four measures that are commonly used to assess the impact of a cancer in the general population. The **incidence rate** is the number of new cases per year per 100,000 persons. The **death** (or **mortality**) **rate** is the number of deaths per year per 100,000 persons. The **survival rate** is the proportion of patients alive at some point subsequent to the diagnosis of their cancer. The **prevalence count** is the number of people alive that have ever been diagnosed with a cancer. All four measures are employed in this report. The Surveillance, Epidemiology, and End Results (**SEER**) Program (*http://seer.cancer.gov*) (based within the Surveillance Research Program (**SRP**) at the National Cancer Institute (**NCI**)) collects incidence and survival data for all areas that participate in the Program. The National Center for Health Statistics (**NCHS**) provides mortality data for the entire United States (**US**). All incidence and mortality rates in this report are age-adjusted (see below) to the 2000 US standard population (see Appendix) unless otherwise specified. Age-adjustment minimizes the effect of a difference in age distributions when comparing rates. Data are presented for a wide spectrum of cancers.

The annual *SEER Cancer Statistics Review* (***CSR***), containing the most recent incidence, mortality, prevalence, and survival statistics, is published by the Cancer Statistics Branch of the NCI. The scope and purpose of the *CSR* follow a report to the Senate Appropriations Committee (Breslow, 1988), which recommended that a broad profile of cancer be presented regularly to the American public. This *CSR* includes incidence, mortality, prevalence, and survival data from 1975 through 2004, the most recent year for which data are available. Observed incidence data for the most recent years may not be complete. Therefore, delay adjusted rates are presented to compensate for this problem (see Reporting Delay).

While most of the rates in this publication have been age-adjusted to the 2000 US standard population, some previous SEER publications have used the 1970 US standard million population. Therefore, rates given in this publication cannot be compared to rates given in those publications. This change conforms to a new federal policy for reporting disease rates and it allows for the age-adjusted rate to more accurately reflect the current age distribution and burden of cancer.

Since 1996, the *CSR* has been available (in .pdf format) at *http://seer.cancer.gov*. This edition can be found at *http://seer.cancer.gov/Publications/CSR1975_2004/*. The website allows timely distribution of the *CSR*. Additional SEER data can be obtained via ***FastStats*** (*http://seer.cancer.gov*) or ***Cancer Query Systems***, an interactive system at *http://seer.cancer.gov/canques*, which allows the user to access over 10,000,000 cancer statistics. The SEER limited-use file with ***SEER*Stat*** software can be used over the internet, or the user can order a CD-ROM version at *http://seer.cancer.gov/publicdata/options.html*. (This URL will soon change to *http://seer.cancer.gov/data/options.html*.) *SEER*Stat* provides a user-friendly PC desktop system for the production of a myriad of cancer statistics, such as incidence rates and survival rates, for various demographic and medical input variables.

Excluded cancers: Some cancers were excluded from most of the analyses. Myelodysplastic syndromes (MDS), for example, was reclassified in ICD-O-3 (effective diagnosis year 2001) from nonmalignant to malignant; other cancers so reclassified include papillary ependymoma, papillary meningioma, polycythemia vera, chronic myeloproliferative disease (NOS), myelosclerosis with myeloid metaplasia, essential thrombocythemia, refractory anemia, refractory anemia with sideroblasts, refractory anemia with excess blasts, and refractory anemia with excess blasts in transformation. In contrast, borderline tumors of the ovary were reclassified from malignant to nonmalignant at the same time. In addition, benign brain/CNS tumors were collected beginning for 2004 diagnoses. All of these cancers were excluded from most of the analyses, especially time trends. Pilocytic astrocytoma, although reclassified in ICD-O-3, was not excluded. Separate tables for MDS and benign brain/CNS are shown.

O-2. THE SEER PROGRAM

The National Cancer Act of 1971 mandated the collection, analysis, and dissemination of data useful in the prevention, diagnosis, and treatment of cancer. This mandate led to the establishment of the SEER Program. The population-based cancer registries participating in NCI's SEER Program routinely collect data on all cancers occurring in residents of the participating areas. Trends in cancer incidence and patient survival in the US are derived from this database.

The SEER Program is a sequel to two earlier NCI programs—the End Results Program and the Third National Cancer Survey. The initial SEER reporting areas were the States of **Connecticut**, **Iowa**, **New Mexico**, **Utah**, and **Hawaii**; the metropolitan areas of **Detroit**, Michigan, and **San Francisco-Oakland**, California; and the Commonwealth of Puerto Rico. Case ascertainment began with January 1, 1973, diagnoses.

In 1974-1975, the program was expanded to include the metropolitan area of New Orleans, Louisiana, the thirteen-county **Seattle-Puget Sound** area in the State of Washington, and the metropolitan area of **Atlanta**, Georgia. New Orleans participated in the program only through the 1977 data collection year. In 1978, ten predominantly African-American counties in **rural Georgia** were added. **American Indian residents of Arizona** were added in 1980. In 1983, four counties in New Jersey were added with coverage retrospective to 1979. New Jersey and Puerto Rico participated in the program until the end of the 1989 reporting year. The National Cancer Institute also began funding a cancer registry that, with technical assistance from SEER, collects information on cancer cases among **Alaska Native** populations residing in Alaska. In 1992, the SEER Program was expanded to increase coverage of minority populations, especially Hispanics, by adding **Los Angeles County** and four counties in the **San Jose-Monterey** area south of San Francisco. In 2001, the SEER Program expanded coverage to include **Kentucky, Greater California** (the counties of California that were not already covered by SEER), **New Jersey,** and **Louisiana**.

The long-term incidence trends and survival data for this report are from five states (Connecticut, Hawaii, Iowa, New Mexico, and Utah) and four metropolitan areas (Detroit, Atlanta, San Francisco-Oakland, and Seattle-Puget Sound) (Fig. I-1); this set of registries is called the **SEER 9**. Additional tables show more recent incidence trends for the **SEER 13** areas (the 9 areas above plus Los Angeles, San Jose-Monterey, Alaska Native Registry, and rural Georgia) since 1992. Other tables give statistics for the **SEER 17** areas; these are the SEER 13 plus Kentucky, Greater California, New Jersey, and Louisiana.

The participating regions were selected principally for their ability to operate and maintain a population-based cancer reporting system and for their epidemiologically significant population subgroups. With respect to selected demographic and epidemiologic factors, they are when combined a reasonably representative subset of the US population. Data from the 9, 13, or 17 SEER geographic areas are used in this report; the given areas contain, respectively, approximately 9,14, or 26 percent of the US population. By the end of the 2004 diagnosis year, the database of 13 SEER and 4 expansion registries (plus Arizona Indians) contained information on **7,032,878** cases diagnosed since 1973. New cases added in the most recent data year (not including Arizona Indians) numbered **374,022**.

The goals of the SEER Program are:

(1) to assemble and report, on a periodic basis, estimates of cancer incidence, mortality, survival, and prevalence in the US;

(2) to monitor annual cancer incidence trends to identify unusual changes in specific forms of cancer occurring in population subgroups defined by geographic and demographic characteristics;

(3) to provide continuing information on trends over time in the extent of disease at diagnosis, trends in therapy, and associated changes in patient survival; and

(4) to promote studies designed to identify factors amenable to cancer control interventions, such as: (a) environmental, occupational, socioeconomic, dietary, and health-related exposures; (b) screening practices, early detection and treatment; and (c) determinants of the length and quality of patient survival.

Incidence and survival data: The SEER Program contracts with nonprofit, medically-oriented organizations having statutory responsibility for registering diagnoses of cancer among residents of their respective geographic coverage areas. Each SEER contractor:

(1) maintains a cancer information reporting system;

(2) abstracts records for *resident* cancer patients seen in every hospital both inside and outside the coverage area;

(3) abstracts all death certificates of *residents* (dying both inside and outside the coverage area) on which cancer is listed as a cause of death;

(4) strives for complete ascertainment of cases by searching records of private laboratories, radiotherapy units, nursing homes, and other health services units that provide diagnostic service;

(5) registers all in situ and malignant neoplasms (with the exceptions of certain histologies

for cancer of the skin and—beginning in 1996—in situ neoplasms of the cervix uteri);

(6) records data on all newly diagnosed cancers, including selected patient demographics, primary site, morphology, diagnostic confirmation, extent of disease, and first course of cancer-directed therapy;

(7) provides active follow-up on all living patients (except for those with in situ cancer of the cervix uteri);

(8) maintains confidentiality of patient records;

(9) semiannually submits electronically to NCI data on all reportable diagnoses of cancer made in residents of the coverage area.

For 1992 to 2000 diagnoses, the SEER program codes site and histology by the *International Classification of Diseases for Oncology*, second edition (**ICD-O-2**) (Percy, Van Holten, & Muir, 1990). All cases before 1992 were machine-converted to ICD-O-2. Beginning with 2001 diagnoses, cases have been coded according to the third edition (**ICD-O-3**) (Fritz et al., 2000). The primary site groupings used for incidence are found in the Appendix. Changes were made to the site recode for ICD-O-2 for comparability with cases coded to ICD-O-3. Follow-up rates are also in the Appendix.

Mortality data: The SEER Program annually obtains from the NCHS a public-use file containing information on all deaths occurring in the US by calendar year. Information on each death includes age at death, sex, geographic area of residence, and underlying and contributing causes of death. For this publication, only the underlying cause of death is used in the calculation of mortality rates. Cause of death for 1969-1978 was coded according to ICD-8; for 1979-1998, ICD-9 was used; beginning with deaths in 1999, ICD-10 was used. Mortality rates for the SEER geographic areas, for each state, and for the entire US are obtained from these data. A list of the mortality site groupings used in this publication is in the Appendix and reflects updates made in 2004.

Numbers of estimated cancers and deaths in 2007: The SEER Program has obtained from the American Cancer Society (**ACS**) projections of the numbers of cancer cases and cancer deaths in the US in 2007 (American Cancer Society, 2007). The ACS projects incidence in 2007 based on incidence rates for 1995-2003 from 41 states, representing about 86% of the US population, that belong to the National Program of Cancer Registries to the 2007 estimated US population (Jemal et al., 2007).

Population data: The population estimates used in the SEER*Stat software to calculate cancer incidence and mortality rates for this report are a modified version of the annual time series of July 1 county population estimates by age, sex, race, and Hispanic origin that are produced by the Population Estimates Program of the US Census Bureau (*http://www.census.gov/popest/estimates.php*) with support from the NCI through an interagency agreement. Descriptions of the methodologies employed by the Census Bureau for various sets of estimates may be found on the same website. County population estimates for 2000 and later years must be bridged from 31 race categories used in Census 2000 to the four

race categories specified under earlier OMB standards in order to report long-term cancer trends. The bridging methodology was developed by the National Center for Health Statistics and is described in a report (Ingram et al., 2003) and on their website *http://www.cdc.gov/nchs/about/major/dvs/popbridge/popbridge.htm*.

Modifications made by the NCI to the population estimates are documented in "Population Estimates Used in NCI's SEER*Stat Software" (*http://seer.cancer.gov/popdata/methods.html*) and the population data files are available for download (see "Download US Population Data" from *http://seer.cancer.gov/popdata/download.html*). Several of the modifications pertaining to the grouping of specific counties were needed to assure the compatibility of all incidence, mortality and population datasets. Another modification affects only population estimates for the State of Hawaii. Based on concerns that the native Hawaiian population has been vastly undercounted in previous censuses, the Epidmiology Program of the Hawaii Cancer Research Center has recommended an adjustment to the populations for their state. The "Hawaii-adjustment" to the Census Bureau's estimates has the net result of reducing the estimated white population and increasing the estimated Asian and Pacific Islander population for the state. The estimates for the total population, black population, and American Indian and Alaska Native populations in Hawaii are not modified.

Starting this year, the 2000-2004 cancer incidence and mortality rates for American Indians and Alaska Natives (AI/AN) are based on the geographic areas (counties) included in the Indian Health Service's Contract Health Service Delivery Area (CHSDA). This reflects a concern that previously reported AI/AN rates were underestimated due to racial/ethnic misclassification of American Indian cases in geographic areas outside of CHSDA. This change has the net effect of higher, and more accurate, incidence and mortality rates for this population.

2000 US standard population: Starting with the November 2004 SEER submission of data (diagnoses through 2002), the SEER Program age-adjusts using the 2000 US standard population based on single years of age from the Census P25-1130 series estimates of the 2000 US population (Day, 1996). For the *CSR*, 19 age groupings were used for age-adjustment: <1, 1–4, 5–9, ... , 80–84, 85+.

O-3. SUMMARY TABLES

While there are detailed tables in separate sections for each of the major cancer sites, information on some rare cancers can be found in the summary tables of section I. For a detailed list of primary sites, the summary tables provide incidence and death rates for the most recent 5-year period, trends (percent change (PC) and annual percent change (APC)) from 1975 to the most recent year, median age at diagnosis, median age at death, and survival rates. The information is provided by race (all races, whites, blacks) and by sex.

O-4. LONG-TERM TRENDS, 1950-2004

Trends in cancer mortality from 1950 to 2004 are summarized by age both for all cancers combined and for lung cancer (Table I-2). These mortality data are based on experience in the entire US. Summaries of long-term trends back to 1950 in cancer incidence and survival are currently not shown.

Use caution when interpreting these statistics. Evaluating trends over a long period of time may hide recent changes in the trends.

O-5. YEARS OF LIFE LOST DUE TO PREMATURE DEATH FROM VARIOUS CAUSES

Death rates alone give an incomplete picture of the burden that deaths impose on the population. Another measure, which adds a different dimension, is the years of life lost due to premature death. This shows the extent to which life is cut short by a particular cause or disease.

This measure is estimated by linking life table data to each death of a person of given age and sex. The life table permits a determination of the number of additional years an average person of that age, race, and sex would be expected to live. In this report, the age groups used in the calculation were 1-year intervals. These remaining years of life left are summed over all deaths due to a particular cause, yielding the estimate of the number of person-years of life lost (**PYLL**). The average years of life lost (**AYLL**) is obtained by dividing the PYLL by the number of deaths. Both of these measures can be calculated for any cause of death.

O-6. CANCER PREVALENCE

Methods: In this report prevalence is calculated at 1/1/2004. **Limited-duration prevalence** is calculated using the counting method implemented in the SEER*Stat software. This method calculates the number or proportion of people alive at the prevalence date who had a diagnosis of the disease within the past *x* years (e.g., *x* = 5, 10, 20, or the full history of the registry). This method includes a correction for people lost to follow-up. For each individual lost to follow-up, a probability of being alive at the prevalence date is estimated from an appropriate survival function stratified by age at diagnosis (0–59, 60–69, 70+), sex, cancer site, year of diagnosis, and race, conditional on being alive at the time of loss to follow-up. Year of diagnosis is stratified into 5-year groups from the prevalence date, with the least recent interval being of varying length (4-8 years), depending on the length of years used to calculate prevalence. Race is stratified into white, black, other (American Indian/Alaska Native, Asian/Pacific Islander), and unknown/other-unspecified. When we use the SEER 11 registries, the same stratification as before is used, with American Indian/Alaska Native separated from Asian/Pacific Islander. Prevalence calculations for Hispanics use race stratified into: white, non-white, and unknown.

Because SEER has available information for the various racial/ethnic groups for different

numbers of years, different years and registries were used to estimate prevalence. Prevalence estimates for all races combined, for whites, and for blacks use cases from 1975 through 2003 from the SEER 9 registries; prevalence estimates for Asian Pacific Islanders and Hispanics use cases diagnosed from 1990 through 2003 from the SEER 11 areas and rural Georgia.

Different methods can be used to determine which tumors are to be included for people diagnosed with multiple tumors. Unless otherwise specified, prevalence calculations included only the *first malignant tumor per person*; that is, in situ cancers and second-or-later primary cancers were not included. Thus, if a woman had a melanoma prior to a breast cancer diagnosis, her melanoma would contribute to the prevalence of melanoma and to the prevalence of all sites, but the breast cancer would not contribute to the prevalence of breast cancer. Counting only one cancer per individual avoids some ambiguity in prevalence counts, and allows the counts for individual sites to sum to the all sites total. Prevalence using different selection criteria is compared in a table in the overview chapter. For more information on tumor selection criteria refer to *http://srab.cancer.gov/prevalence/methods.html*.

Complete prevalence is an estimate of the number of persons (or the proportion of population) alive on a specified date who had been diagnosed with the given cancer, no matter how long ago that diagnosis was. It was estimated for all races, whites, and blacks by applying the *completeness index method* (Capocaccia & De Angelis, 1997; Merrill et al., 2000; Mariotto et al., 2002) to limited-duration prevalence. The completeness index method is implemented in the COMPREV software (*http://srab.cancer.gov/comprev/*). Validation of the completeness index for all races and for whites was made by using data from the Connecticut Tumor Registry (CTR) beginning with 1940; for blacks, SEER 9 data beginning with 1975 were used. Identification of blacks is not possible in the CTR data prior to 1970. To validate the completeness index for blacks, we have compared the performance of the method to obtain 24-year prevalence from 10-year limited-duration prevalence. For all races combined and for whites, in cases where the validation indicated some lack of fit of the model, an approximation to the completeness index was derived from the CTR data. If there was a lack of fit for blacks, no estimate of complete prevalence was reported. Complete prevalence for Asian/Pacific Islanders and Hispanics is not available at this time. Complete prevalence by age for all races combined was validated by comparing estimated 10-year complete prevalence with observed prevalence from the CTR data. Prevalence by age is reported for the sites that validated well.

The US cancer prevalence counts at 1/1/2004 *were estimated* by multiplying the SEER age- and race-specific prevalence proportions by the corresponding US population estimates based on the average of 2003 and 2004 population estimates from the US Bureau of the Census. US cancer prevalence counts for all races were estimated by summing the US estimated counts for whites/unknown, blacks, and other races. For Hispanics, the estimates for Hispanics of white or unknown race and for Hispanics of other races were summed.

Limited-duration prevalence proportions by age at prevalence are not shown for childhood cancers (diagnosis before age 20) since many of these estimates are not informative. (For

example, the number of people diagnosed with childhood cancers in the last 25 years and who are currently age 50-59 is zero by definition.) While it is of interest to estimate the total number of Americans currently alive who were diagnosed with a childhood cancer, the limitations of the duration of the SEER cancer registries requires that this be estimated using statistical modeling. (This work is in progress.)

For more details on available prevalence estimates, see *http://srab.cancer.gov/prevalence/index.html*.

Results and Table Description: The total number of persons alive on January 1, 2004, in the US who had had a diagnosis of invasive cancer is now estimated to be **10,762,214**. Compared with last year's 2003 prevalence estimate of **10,495,985** persons, this year's 2004 estimate represents an increase of **266,229** cases. This increase is due to increases in incidence, improvements in survival, and the increase and aging of the US population. The overview chapter contains two prevalence tables. The first table reports US complete prevalence counts by age at prevalence and sex for some cancer sites. The second table reports US prevalence counts for people diagnosed in the 5 years and 29 years prior to the prevalence date using different tumor inclusion criteria. Each site-specific chapter contains a prevalence table that reports limited-duration US prevalence counts by time since diagnosis for different racial/ethnic groups. US complete prevalence estimates are also reported when available. The second part of the table displays the percent of the population in the SEER 11 areas diagnosed in the previous 10 years with the specific cancer by 10-year age groups for the different racial/ethnic groups.

O-7. PROBABILITY OF BEING DIAGNOSED WITH OR DYING FROM CANCER

Each site-specific section contains a table showing the probability (expressed as a percent) of a person of a specified race, sex, and age (0, 10, 20, 30, 40, 50, or 60) being diagnosed with the specified invasive cancer within the next 10, 20, or 30 years, or within their remaining lifetime. Lifetime risks of being diagnosed with invasive cancer and lifetime risks of dying from cancer also appear (as percents) in each table. There are summary tables of lifetime risk in the overview.

Lifetime and interval risks of being diagnosed with cancer: The probability of being diagnosed with cancer is computed by applying cross-sectional age-specific 2002-2004 incidence rates from the SEER 17 areas and death rates from the entire US to a hypothetical cohort of 10,000,000 live births. This cohort is considered to be at risk for two mutually exclusive events: (1) developing the specified cancer, and (2) dying of other causes without developing the specified cancer. Using these two types of events, a standard **multiple decrement life table** (with 20 age groups from 0-4 to 90-94 and 95+) is derived. For each age interval, the number alive and free of the specified cancer at the beginning of the interval is decremented by the number who develop the specified cancer and the number who die of other causes. The lifetime risk of being diagnosed with the specified cancer is derived by summing all

cancer cases from age 0-4 through age 95+ and dividing by 10,000,000. This calculation does not assume that an individual lives to any particular age; rather, it is the sum over all age intervals of the probability of living to the beginning of that interval without developing the given cancer times the probability of developing the cancer in that interval. The probability of developing cancer during any time period (e.g., between age 50 and age 60) is calculated by adding up all the cancers in the life table over the specified age range and dividing by the number of individuals alive and free of the specified cancer at the beginning of the period. The methodology is described in detail in Fay (2003, 2004). To improve the precision of the calculations, rates were calculated beyond the usual last open ended age interval (i.e. 85+) for the age groups 85-89, 90-94, and 95+.

Lifetime risk of dying from cancer: The lifetime risk of dying from a specified cancer is derived using a standard multiple decrement life table (Elandt-Johnson & Johnson, 1980). For each age, the risks of dying of the specified cancer and of all other causes are calculated, based on mortality data from the entire United States. The estimates of developing and dying from cancer are implemented in DevCan (Probablity of DEVeloping or dying from CANcer software). More details on the software, various databases, and the methodology can be found at *http://srab.cancer.gov/devcan/.*

O-8. U.S. CANCER DEATH RATES BY STATE

Each cancer-site-specific section presents the death rate for the given cancer for each state and the District of Columbia, specifying the five highest and the five lowest death rates by state for the most recent 5-year period for all persons, males only, and females only. The rates are per 100,000 persons; they are age-adjusted to the US 2000 standard million population. (In some previous editions of the CSR, the 1970 US standard million population was used; therefore, *death rates in this edition cannot be compared to the rates in those editions.*)

The **percent difference (PD)** between a state rate and the rate for the total US is given by the formula:

$$PD = \frac{\text{(State Rate} - \text{Total US Rate)}}{\text{Total US Rate}} * 100$$

The **standard error** for each age-adjusted state rate is calculated, based on the assumptions that (1) for each age-specific rate, the number of deaths is a Poisson random variable (Keyfitz, 1966) and (2) the variance of the age-adjusted rate is a linear combination of the variances of the age-specific rates (Snedecor & Cochran, 1980; pp. 188-9).

The **standard error of the difference** (SE_d) between a state rate and the total US rate is given by the formula

$$SE_d = \sqrt{SE_S^2 + SE_U^2 - 2Cov_{S,U}}$$

where SE_S and SE_U are the standard errors of a state rate and of the total US rate, respectively, and $Cov_{S,U}$ is the covariance between the two rates. The variance of each rate (i.e., the square of the standard error) and the covariance between the two rates are based on the Poisson assumption. The standard error does not represent the total error that may be present in the age-adjusted rate; it is merely the square root of the variance associated with the rates. In addition to this variance, there also exist potential biases and errors in the measurement of the rate that are difficult to assess accurately and probably impact differently on the error calculations for different states.

The difference between each age-adjusted state rate and the age-adjusted US rate is tested for statistical significance (see below) by calculating a Z (standard normal) statistic from the formula:

$$Z = (\text{State rate} - \text{Total US rate}) / SE_d$$

Although the rates being compared are not independent because each state is part of the US, the statistical test may not be substantially affected if the state represents a small proportion of the total US. There is also an adjustment for multiple comparisons; see below under *Statistical Significance*.

O-10. JOINPOINT REGRESSION ANALYSIS OF CANCER TRENDS

A recent advance in the presentation of cancer trends is the use of joinpoint models (Kim et al., 2000). In some past issues of the *Cancer Statistics Review*, certain time intervals (e.g., 1973–1996) were specified and the annual percent changes (APC) were computed over those intervals. The choices of where to start and where to end an interval were arbitrary and sometimes did not give an accurate picture of the trend for a given cancer site. For example, the rates might be increasing and decreasing in different parts of the same interval. For some sites, increases occurred in the earlier years, followed by declines in more recent years.

To achieve greater descriptive accuracy, a statistical algorithm the finds the optimal number and location of places where a trend changes. The point (in time) where a trend changes is called a **joinpoint**. Trends may change in different ways at a joinpoint: from up to down, from down to up, from up to up at a different rate, or from down to down at a different rate. A **joinpoint regression model** describes the trends by a sequence of connected segments where each segment is connected by a straight line on a log scale. Adjacent segments are connected at a joinpoint. The segments are connected because we assume that rates generally change smoothly, rather than "jump" abruptly. The rates are assumed to grow or decay exponentially, i.e., to change by a constant percentage each year. Thus the slope in each segment can be associated with a fixed annual percent change (**APC**).

Joinpoint analysis first assumes no joinpoints are needed to describe the data accurately, i.e., the trend over the entire interval 1975-2004 does not change. Joinpoints are added in turn if they are statistically significant. Thus, in the final model, each joinpoint represents a significant change in trend. Computational considerations currently limit the maximum possible number of

segments to be no larger than four, with three joinpoints. Smoother polynomial models may provide a good fit overall, but are less sensitive to what is occurring at the ends of the data .

In running the Joinpoint program, we set the program parameters as follows: maximum number of joinpoints 3, minimum interval between joinpoints 2 years, minimum interval between a joinpoint and an endpoint 2 years, joinpoints occurring only at exact years. These restrictions provide some added stability to the resultant models. Different values for these parameters may yield a different joinpoint model. Since the test statistic to determine if additional joinpoints are necessary cannot be compared against any known standard distribution to determine significance, (e.g., the normal, t, or f) a permutation test is used which simulates the distribution of the test statistic under the null hypothesis. Thus an element of randomness is introduced by the random number stream used. However, for greater consistency in the p-values obtained if one were to change the random seed for each run, we run the program for 4499 permutations.

A Windows-based program, *Joinpoint*, is freely available at *http://srab.cancer.gov/joinpoint/*; it accepts data from the *SEER*Stat* program, as well as user defined data. Further details on joinpoint regression may be found at the web site.

O-11. REPORTING DELAY

Timely and accurate calculation of cancer incidence rates is hampered by **reporting delay**, the time lapse before a diagnosed cancer case is reported to the NCI or the delay in receiving updated information for an existing case. Currently, the NCI allows a standard delay of 22 months between the end of the diagnosis year and the time the cancers are first reported to the NCI in November, almost two years later. The data are released to the public in the spring of the following year. For example, cases diagnosed in 2004 were first reported to the NCI in November 2006 and released to the public in April 2007. However, in each subsequent release of the SEER data, *records from all prior diagnosis years* (e.g., diagnosis years 2003 and earlier in the 2006 submission to the NCI) *are updated* as either new cases are found or new information is received about previously submitted cases. The submissions for the most recent diagnosis year are, in general, about two percent below the total number of cancers that will eventually be submitted for that year, although this varies by cancer site and other factors. The idea behind modeling reporting delay is *to adjust the current case count to account for anticipated future corrections (both additions and deletions) to the data*. These adjusted counts and the associated delay model are valuable in more precisely determining current cancer trends, as well as in monitoring the timeliness of data collection—an important aspect of quality control (Clegg et al., 2002). Reporting delay models have been previously used in the reporting of AIDS cases (Brookmeyer & Damiano, 1989; Pagano et al., 1994; Harris, 1990).

In this report, we show SEER age-adjusted incidence rates and trends, along with their calculated delay adjustments for all cancers combined (malignant only except for urinary bladder), for female breast in situ, for urinary bladder (in situ and malignant), and for 22 malignant cancer sites: melanoma (for all races combined and whites only), lung/bronchus,

colon/rectum, prostate, female breast, liver and intrahepatic bile duct, pancreas, cervix uteri, corpus and uterus, ovary, testis, kidney and renal pelvis, brain and other nervous system, Hodgkin lymphoma, non-Hodgkin lymphoma, all leukemias, esophagus, larynx, myeloma, oral cavity and pharynx, thyroid, and stomach.

Cancer data from diagnosis years of 1981 to 2004 were used to model reporting delay distribution. A delay distribution models the probability of a cancer being reported after a delay of d years (d = 2, 3, ...,25). The number of cancers reported at each delay year is assumed to follow a Poisson distribution. Cases are removed as corrections to the data are made, and the probability of removing cases is modeled as a binomial distribution. To reduce the number of parameters that have to be estimated and to achieve stability in the tails of the delay distributions, an assumption is made that all cancer cases will be reported within 25 years of diagnosis.

The delay distributions were modeled as a function of covariates using a discrete-time proportional hazards model. For the models presented here the following potential covariates are included: age at diagnosis, sex, diagnosis year, delay time, and race. Age at diagnosis was modeled as a 3-category variable with levels 0–49, 50–64, and 65+. Diagnosis year was modeled either as a continuous covariate or as categorized variables: 1981–1985, 1986–1990, and 1991–2004. Delay time d was modeled as a categorical variable in one of three ways:
(1) $d > 2$ or $d > 3$,
(2) $d > 2$, $d > 3$, $d > 4$, or $d > 5$, and
(3) $d > 2$, $d > 3$, ... , or $d > 10$.
For each cancer site, a delay distribution was calculated for all races combined and separate delay distributions were calculated for whites and for blacks. When modeling delay distributions for all races combined, if a patient's race value changed between two submission years the change of value does not contribute to the delay distribution. For melanoma, only all races combined and whites were analyzed because melanoma is rare for blacks.

Maximum likelihood estimates of delay probabilities were obtained using the Newton-Raphson algorithm. Details of the estimation can be found in Midthune et al. (2005). For each of the cancer sites, up to 72 models of pre-determined combinations of covariates were considered. We evaluated these models by fitting the models using data of diagnosis years between 1981 and 2003 and then predicting the cancer counts for 2004. For each cancer site, the model that minimized the sum of squared prediction errors was chosen as the default model. An algorithm was then used to compare the default model with competing models in order to select a model that best balanced prediction and simplicity. The chosen model was then refitted using all data (1981–2004 diagnosis years) to estimate delay distributions and calculate delay-adjusted estimates of the cancer counts.

Age-adjusted (using the 2000 US standard population) cancer incidence rates were then calculated with and without adjusting for reporting delay. Joinpoint linear regression (Harris, 1990) was used to obtain the annual percentage changes for the 1975–2004 incidence rates for

the data series with and without delay adjustment. Because the delay distribution was assumed complete after 25 years, incidence rates for diagnosis years prior to 1981 are not adjusted. In these joinpoint regression analyses, up to three joinpoints (i.e, four trend-line segments) were allowed, and these were modeled to fall at either whole years or midway between diagnosis years. Joinpoints were constrained to be at least two years away from both the beginning and the end of the data series and at least two years apart. Joinpoint regressions were fitted using the weighted-least-squares (weighted by appropriate variances of age-adjusted incidence rates) option in the *Joinpoint* regression software.

Results show that adjusting for delay tends to raise cancer incidence rates in more current reporting years. While this adjustment increases the rate of change over the most recent diagnosis years, it probably will only rarely cause the detection of a new joinpoint, although this is possible. See Clegg et al. (2002) for details on the impact of reporting-delay adjustment to SEER cancer incidence rates.

For estimates of delay-adjusted rates, delay-adjustment factors, description of the covariates included in each cancer site model, and other details of delay adjustment, see *http://srab.cancer.gov/delay/*. The estimates of the delay-adjusted rates are in the Cancer Query Systems (*http://seer.cancer.gov/canques/*).

O-12. STATISTICAL SIGNIFICANCE

Errors may be made in the estimation of a given statistic. In order to test whether two groups (such as the populations of a state and the entire US) have the same or different *actual* rates, the *observed* rates for the groups are compared. Statisticians consider that a difference in observed rates can be explained by one of two hypotheses: (H_0) The actual rates are really the same, but the observed rates are different because of some combination of error-causing factors, or (H_1) the actual rates of the groups are really different. H_0 is called the **null hypothesis** (because it says there is *no* real difference); H_1 is called the **alternate hypothesis**. Typically, H_0 is rejected only if there is strong evidence in favor of H_1. (Thus, if the observed rates are equal, we cannot reject H_0.)

Using statistical theory, one can determine the distribution of the rate difference under the assumption that H_0 is true. Then values of the rate difference that are very unlikely to occur if H_0 is true are identified. More specifically, a small positive number, called **alpha** (α), is chosen; usually, α is 0.05 or 0.01. (Alpha is called the **significance level** of the hypothesis test.) One can then identify limits for the difference in rates such that, if H_0 is true, the probability of the difference being outside of those limits is α. If the observed difference is *outside* of these limits, then the observed result is *very unlikely* to happen if H_0 is true, so H_0 is rejected.

Another way of looking at the same process is to calculate, assuming H_0 is true, the probability that the observed difference or any greater observed difference would occur; this number is called the ***P*-value** of the observed result. If the *P*-value of a comparison is less than α (that is,

the observed difference is *very unlikely* to happen if the null hypothesis is true), H_0 will be rejected. If the *P*-value of a test is greater than the significance level α, H_0 will not be rejected. When a difference in rates is sufficiently large to cause the null hypothesis to be rejected for a given value of α (usually 0.05), it is called a **statistically significant** difference.

When a null hypothesis is rejected, there remains a small chance that a wrong decision has been made. If many statistical comparisons are done, even with $\alpha = 0.01$, the chance of making at least one wrong decision becomes a concern. In testing the differences between the total US rate and the rate for each state (or for the District of Columbia) for a given cancer, 51 statistical comparisons of the type described above are performed. Based on one of Bonferroni's inequalities (if there are n events and p_i is the probability of success in event i, then $P(\text{at least 1 success}) < p_1 + ... + p_n$) (Snedecor & Cochran,1980; p. 115-117), the significance level α for each individual comparison was set equal to $0.01/51 \approx 0.0002$. Thus, only individual-state-to-total-US comparisons with an associated *P*-value less than 0.0002 are considered to be statistically significant. That is, a *very small* significance level α (0.0002) is used in order to minimize the total risk (0.01) of falsely deciding that some pair of equal rates are unequal.

Use caution in assessing statistically significant differences. Population size has an important role in any calculation of statistical significance. Some states may have estimated rates that are very close to the estimated total US rate, but because of their large population, the difference between their estimated rate and the estimated total US rate is found to be statistically significant. In this case, the true state rate and the true US rate are almost certainly different, because the observed difference, though small, is nearly impossible if the null hypothesis (equal rates) is true. A small difference in rates, however, may have no practical importance. On the other hand, some smaller states may have estimated rates that differ substantially from the estimated total US rate, but because of their relatively small population, the differences are found to be statistically nonsignificant. When this happens, if the true state rate and the true US rate were equal, the probability of obtaining a difference at least as large as what has been observed is greater than $\alpha \approx 0.0002$. Therefore, *because the evidence against it isn't strong enough, the null hypothesis (equal rates) is not rejected.*

If the percent difference (PD) between the two rates is small, there may be some question about the importance of the difference. It is difficult to specify a minimally significant absolute PD, below which the difference would always be unimportant, because the observed PD will depend on the populations of the areas involved. It may be of value to consider the size of the PD between a state rate and the US rate in assessing the importance of a statistically significant difference.

Comparing individual state rates with the US rate and assessing statistical significance is not an appropriate procedure for assessing geographic clustering of state rates. Identification of states which may represent regional clusters of high or low rates would require additional statistical and graphical analyses.

For a number of cancers, the District of Columbia has the highest death rates. *Use caution when comparing cancer rates for the District with those from the 50 states.* The District is an entirely urban area, whereas a state includes urban, suburban, and rural areas. Mortality rates for many cancers are higher in urban areas. Also, the District has a higher percentage of blacks (about two-thirds) than any state; their higher mortality rates for several types of cancer elevate the overall rate for the District.

O-13. INTERPRETATION OF CANCER STATISTICS

When reviewing the various cancer incidence, mortality, and survival statistics provided in this report, be aware that a number of factors may affect the interpretation of many of these statistics.

Survival rates for all cancers combined: The mix of cancers changes over time as the incidence of some cancers increases and the incidence of others decreases. Thus, in calculating the survival rate for all cancers combined, the proportions corresponding to the specific cancers will also change over time. Therefore, the overall cancer survival rate can fluctuate even when the survival rates for site-specific cancers remain unchanged. (While it is possible to adjust the survival rate for all cancers combined on the basis of the relative frequency of each specific cancer in some specified reference period, rates adjusted in this manner differ by only a small amount from unadjusted rates. In the future, such an adjustment may become more important if there are substantial changes in the incidence of various cancers.)

Early detection/screening: The improved earlier detection and diagnosis of cancers may produce an *increase* in both incidence rates and survival rates. These increases can occur as a result of the introduction of a new procedure to screen subgroups of the population for a specific cancer; they need not be related to whether use of the screening test results in a decrease in mortality from that cancer. As the proportion of cancers detected at screening increases, presumably as a result of increased screening of the population, patient survival rates will *increase*, because they are based on survival time *after diagnosis*. The interval between the time a cancer is diagnosed by a screening procedure and the time when the cancer would have been diagnosed in the absence of screening is called **lead-time** (Zelen, 1976). (Screening for breast cancer has been demonstrated to result in increased survival over and above that resulting from lead-time alone and to reduce breast cancer mortality. The benefit of screening is being studied for some other cancers.)

If a new screening procedure consistently detects cancer in a preinvasive phase, this may result in a *decrease* in survival rates for *invasive* cancer. In this case, **length-biased sampling** (Zelen, 1976) may be operating. Length-biased sampling would result in the preferential detection—in a *preinvasive* phase—of those cancers that would have had a relatively good prognosis had they progressed to invasive disease; these potentially invasive cancers would be systematically eliminated. If this occurs, the mix of cancers that are not detected at screening

and progress to invasive may become less prognostically favorable, resulting in a *decrease* in survival rates for patients with invasive cancers. (Length-biased sampling may at least partially explain survival trends for cervical cancer. Other cancers possibly affected include breast, colon, rectum, and prostate.)

Changes in diagnostic criteria: Early detection of cancer resulting from either screening or earlier response to symptoms may result in the increasing diagnosis of small tumors that are not yet life-threatening. This may have the effect of raising the incidence and survival rates with little or no change in mortality rates. Breast, colon, prostate, cervix uteri, bladder, and skin (melanoma) are the cancer sites most likely to be affected.

Technological advances in diagnostic procedures: In this report, trends in survival by stage at diagnosis are not presented for specific cancers; trends in stage distributions are presented rarely. However, it is possible to compare survival rates by stage and stage distributions given here with those for earlier time periods (as provided in previous reports or available from the SEER public-use data file). Thus, it is necessary to comment on the effect of technological advances on the diagnosis and staging of cancer.

The assignment of a given stage to a particular cancer may change over time due to advances in diagnostic technology. Introduction of new technology can give rise to a phenomenon known as **stage migration**. Stage migration occurs when diagnostic procedures change over time, resulting in an increase in the probability that a given cancer will be diagnosed in a *more advanced* stage. For example, certain distant metastases that would have been undetectable a few years ago can now be diagnosed by a computer tomography (CT) scan or by magnetic resonance imaging (MRI). Therefore, some patients who would have been diagnosed previously as having cancer in a *localized* or *regional* stage are now diagnosed as having cancer in a *distant* stage. The likely result would be to remove the worst survivors—those with previously undetected distant metastases—from the localized and regional categories and put them into the distant category. As a result, the stage-at-diagnosis distribution for a cancer may become less favorable over time, but the survival rates for each stage may improve: the early stage will *lose* cases that will survive *shorter* than those remaining in that category, while the advanced stage will *gain* cases that will survive *longer* than those already in that category. However, *overall survival would not change* (Feinstein et al., 1985). Stage migration is an important concept to understand when examining temporal trends in survival by stage at diagnosis as well as temporal trends in stage distributions; it could affect the analysis of virtually all solid tumors.

Evolution of stage classifications: Every few years, the American Joint Committee on Cancer produces a new cancer-staging manual (Beahrs, 1988). The evolution of such classifications reflects the identification of new prognostic factors that may influence choice of treatment. The SEER Program collects data on **extent of disease (EOD)** rather than stage; EOD is *more specific* than stage and usually determines stage, even when stage definitions

change. Thus, SEER easily adapts to changes in stage definitions; moreover, trends in a newly redefined stage can usually be calculated.

For those cancers for which new prognostic variables are introduced into staging, so that previously collected EOD data cannot determine new stage categories, there can be problems in assessing trends in stage of disease. Only by reviewing the evolution of staging for a given cancer is it possible to determine what effect changes in stage definitions have had on stage-specific survival and on stage-at-diagnosis distributions. Stage migration (mentioned above) and EOD migration need also be taken into account. One reason for using the historical categories of *localized*, *regional*, and *distant* is that these categories have been fairly consistent over time.

Interpreting relative survival rates: The relative survival rate is the ratio of the observed survival rate to the expected survival rate for a given patient cohort. The expected survival rate is based on mortality rates for the entire population, taking into account, as appropriate, the age, sex, race, and year of diagnosis of the patients. Assuming that the presence of cancer is the only factor that distinguishes the cancer patient cohort from the general population, the relative survival rate approximates the probability that a patient will *not* die of the diagnosed cancer within the given time interval.

A factor related to the risk of a cancer may also be related to the risk of dying from causes unrelated to the cancer. An example of such a factor is *smoking*. Smoking is a major risk factor for lung cancer; therefore, a cohort of lung cancer patients will contain a much higher proportion of smokers than does the general population. However, smoking is also a risk factor for other diseases, resulting in smokers having a shorter life expectancy than nonsmokers. Expected survival rates for lung cancer patients based on the general population will be unduly optimistic for this reason; they will result in relative rates that are *lower* than they should be. The problem cannot be easily corrected because separate life tables for smokers and nonsmokers are not available. Amount of smoking (usually measured in pack-years) is clearly an important variable. The possibility that expected rates may not be appropriate for a given patient cohort should also be considered when examining relative survival rates for patients with cancers of the cervix uteri or breast, because the risk of these cancers has been associated with socioeconomic status (Baquet et al., 1991), which may be related to life expectancy.

Previous to the *CSR* for 1973–1996, the expected rate tables used were for 1970 and 1980; there were separate tables for whites, blacks, American Indians, Chinese, Japanese, Filipinos, white Hispanics, and Hawaiians. In updating the tables for 1990, several problems emerged. The US life tables are based on age, race, and sex information from death certificates. The information on race on the death certificate may not be accurate (Rosenberg et al., 1999). One reason is that funeral directors may inaccurately report race on a death certificate. Also, reported age at death, especially for those older than 85, may not be accurate because birth certificates were not issued with as much regularity in the early 1900s as they are today. Although race misclassification and age-at-death misreporting exist across all races, they may

be more problematic for races other than white or black because of those races' smaller population sizes. Therefore, life tables were generated for 1970, 1980, 1990, and 2000 only for white, black, and other; these life tables were used to produce the relative survival rates in this book. There may be small variations among survival rates calculated in this *CSR* and those in *CSR*s prior to 1973–1996 due to the addition of the 1990 rate table and those in *CSR*s prior to *CSR1975-2004* due to the addition of the 2000 rate table.

Comparison with other databases: The SEER data are obtained from population-based cancer registries covering about 26 percent of the US population. It is sometimes of interest to compare cancer statistics for SEER areas with those from other registries both in the US and worldwide. In making such comparisons, one must carefully consider the factors considered above for both data sources. In addition, one should assess all of the following: (1) completeness of case ascertainment, (2) rules used to determine multiple primaries, (3) follow-up, (4) rules used in assigning and coding cause of death, and (5) the sources and procedures used in obtaining population estimates. Depending on the rates being compared, there could be other confounding factors which should be considered. The same standard or standard million population should be used for the age-adjustment of each group being compared. Examples of other databases are USCS (US Cancer Statistics Working Group, 2005) and CINA+ Online (*http://www.naaccr.org/cinap/index.htm*).

It is sometimes interesting to compare survival data for cancer patients in SEER areas with data from clinical trials. *This must be done with great caution.* Survival data from clinical trials may have been obtained from a patient population that differs from that of SEER patients in prognostic factors for the given cancer; any survival comparisons would have to adjust for such differences. Also, it is necessary to verify that the methodology used in computing survival rates is the same for both data sources. Furthermore, clinical-trials patients may differ from SEER patients in characteristics that may be related to survival but are not recorded in either database. If this were true for a given cancer, it would not be possible to make valid comparisons of this type.

Errors in data collection: In the process of registering cancer patients, errors may be made in abstracting and coding the data, which includes demographic information, cancer site, histology, extent of disease, treatment, and patient survival. Quality control studies are periodically carried out to detect and correct this type of error, but no attempt is made to incorporate this source of error into the variance estimates of cancer rates reported here.

Comparison of this report with previous reports: It is important to note that most rates in this CSR were age-adjusted to the 2000 standard US population; in some previous SEER reports, the 1970 standard million population was used. Therefore, *rates in this report can not be compared to rates and trends in those reports.*

The cancer registries that participate in the SEER Program submit data on all cancers diagnosed in their coverage areas to the NCI each year. Because of the dynamic nature of the

registries' databases, *the reported number of new cancer cases in a particular race-sex-age-cancer category in a given calendar year may change from that which has been reported in a previous publication.* Additional cancer cases that were previously overlooked for a given diagnosis year may have been found and reported to the central registry. There may have been follow-back of cancers diagnosed by death certificate only; successful efforts to establish the dates of diagnosis for such patients will change the number of patients reported for a given diagnosis year. Code changes may occur when a patient dies; for example, information on race is generally available on the death certificate and may be used to update a previously unknown value. There may have been elimination of duplicate records for the same patient, often due to name changes or misspellings.

Thus, a recent report may have a different number of cases for a given diagnosis year than an earlier report, with resulting effects on incidence and possibly survival rates. Population estimates may also change from one report to another for some calendar years. This occurs because the NCI receives population estimates that are regularly updated by the Bureau of the Census (**BOC**); for example, previous population estimates for years beginning with 1990 were replaced with new estimates from the BOC. Such changes may result in some differences between incidence and mortality rates for a given calendar period as published in different reports.

O-14. STANDARD ERRORS OF RATES

Survival rates: In the tables presenting survival rates, the magnitude of the standard error is given as a clue to the reliability of a given rate: the greater the standard error, the less reliable the rate. In addition, if there were fewer than 25 diagnoses in the first interval of the life table constructed to calculate survival, or if all cases became lost to follow-up within an interval, a valid survival rate could not be calculated, as is noted in the table footnotes.

The **standard error** (**SE**) of a relative survival rate is obtained as follows (Ederer et al., 1961):

$$SE(CR_t) = CR_t \cdot \sqrt{\frac{q_1}{e_1 - d_1} + \frac{q_2}{e_2 - d_2} + \ldots + \frac{q_t}{e_t - d_t}}$$

where CR_t is the t-year relative survival rate, and for $i = 1, \ldots, t$,
q_i is the probability of dying in year i after diagnosis,
e_i is the effective number of patients at risk in year i after diagnosis, and
d_i is the number of deaths in year i after diagnosis.

Incidence and mortality rates: The standard errors of age-adjusted incidence and mortality rates are often not specified. However, the reader can approximate the SE of a particular

incidence or mortality rate by the following formula for the SE of a crude incidence or mortality rate (Keyfitz, 1966):

$$SE(\text{rate}) \approx \text{rate} / \sqrt{\text{number of cancer cases or deaths}}$$

Appendix tables provide numbers of cancer diagnoses within SEER areas and numbers of deaths in the entire US, respectively, by race and sex for the most recent 5-year period. These can be used to obtain approximations of the standard errors for associated age-adjusted rates for the same time period using the above formula. To approximate the standard error of a rate for a single year, use the formula but replace the number of cancer cases or deaths with the number of cancer cases or deaths divided by 5.

O-15. DEFINITIONS

Several technical terms are used in presenting the data in this report. Their definitions are presented here to clarify them for the reader.

Incidence rate: The cancer incidence rate is the number of new cancers of a specific site/type occurring in a specified population during a year, usually expressed as the number of cancers per 100,000 persons at risk. That is,

Incidence rate = (New cancers / Population) * 100,000.

The *numerator* of the incidence rate is the number of new cancers; the *denominator* of the incidence rate is the size of the population. The number of new cancers may include multiple primary cancers occurring in one patient. The primary site reported is the site of origin and not the metastatic site. In general, the incidence rate would not include recurrences. *The population used depends on the rate to be calculated.* For cancer sites that occur in only one sex, the sex-specific population (e.g., females for cervical cancer) is used.

The incidence rate can be computed for a given type of cancer or for all cancers combined. Except for 5-year age-specific rates, all incidence rates in this report are *age-adjusted* (see below) to the 2000 US standard population (or, where appropriate, to the world standard million population). (In some previous editions of the *CSR*, the 1970 US standard million population was used; therefore, *incidence rates in this edition cannot be compared to rates published in those editions.*) Incidence rates are for *invasive cancer only*, unless otherwise specified. (Exceptions are the incidence rate for cancer of the urinary bladder (where both in situ and invasive cancers are counted) and breast cancer in situ, which is shown separately.)

Death rate: The cancer death (or mortality) rate is the number of deaths with cancer given as the underlying cause of death occurring in a specified population during a year, usually expressed as the number of deaths due to cancer per 100,000 persons. That is,

Death Rate = (Cancer Deaths / Population) * 100,000.

The *numerator* of the death rate is the number of deaths; the *denominator* of the death rate is the size of the population. As with the incidence rate, *the population used depends on the rate*

to be calculated. The death rate can be computed for a given cancer site or for all cancers combined. Except for 5-year age-specific rates, all death rates in this report are *age-adjusted* (see below) to the 2000 US standard million population (or, where appropriate, to the world standard million population). (In some previous editions of the *CSR*, the 1970 US standard million population was used; therefore, *death rates in this edition cannot be compared to rates published in those editions.*)

Age distribution: A table showing a partition of the entire lifespan into disjoint age intervals, along with the proportion of the population in each interval.

Median age: The age at which half of a population is younger and half is older.

Standard population: A **standard population** for a geographic area, such as the US or the world, is a table giving the proportions of the population falling into the age groups 0, 1-4, 5-9, ..., 80-84, and 85+. A **standard million population** for a geographic area is a table giving the number of persons in each age group 0, 1-4, ... , 85+ out of a theoretical cohort of 1,000,000 persons that is distributed by age in the same proportions as the standard population. Table A-7 shows the US 2000 standard population and the world standard million population. (Some World Health Organization mortality publications use a different world standard million population.)

Age-adjusted rate: An age-adjusted incidence or mortality rate is a weighted average of the age-specific incidence or mortality rates, where the weights are the counts of persons in the corresponding age groups of a standard million population. The potential confounding effect of age is reduced when comparing age-adjusted rates based on the same standard million population. For this report, the 2000 US standard million population (or, where appropriate, the world standard million population) is used in computing age-adjusted rates, unless otherwise noted.

Percent change: The percent change (**PC**) in a statistic over a given time interval is

Percent change = (Final value – Initial value) / Initial value * 100.

A positive PC corresponds to an increasing trend, a negative PC to a decreasing trend.

Annual percent change: The annual percent change (**APC**) is calculated by first fitting a regression line to the natural logarithms of the rates (r) using calendar year (x) as a regressor variable. In this report the method of *weighted least squares* is used to calculate the regression equation. If $\ln(r) = mx + b$ is the resulting regression equation (with slope m), then $APC = 100(e^m - 1)$ A positive APC corresponds to an increasing trend, a negative APC to a decreasing trend.

Because the methods used in their calculation are mathematically different, *the signs of the PC and the APC for a given statistic and time interval may differ*, as occurs in a few of the tables presented. That is, one of these statistics may show an increasing trend, the other a decreasing

trend.

Testing the hypothesis that the actual mean annual percent change is 0 is equivalent to testing the hypothesis that the theoretical slope estimated by the slope m of the line representing the equation $\ln(r) = mx + b$ is 0. The latter hypothesis is tested using the t distribution of m / SE_m with $n - 2$ degrees of freedom. The standard error of m, called SE_m, is obtained from the fit of the regression (Kleinbaum et al., 1988). (This calculation assumes that the rates increased or decreased at a constant rate over the entire calendar year interval; the validity of this assumption was not assessed.) In those few instances where at least one of the rates was 0, the linear regression was not calculated.

Life table: A table for a given population listing, for each sex and each age from 0 to 120, how many members die at that age and how many survive one more year.

Observed survival rate: The observed survival rate represents the proportion of cancer patients surviving for a specified time interval after diagnosis. Note that some of those not surviving died of the given cancer and some died of other causes.

Relative survival rate: The relative survival rate is calculated using a procedure (Ederer et al., 1961) whereby the observed survival rate is adjusted for expected mortality. The relative survival rate approximates the likelihood that a patient cohort will not die from causes associated specifically with the given cancer before some specified time after diagnosis. It is always larger than the observed survival rate for the same group of patients.

Standard error: The standard error of a rate is a measure of the sampling variability of the rate.

Person-years of life lost: The person-years of life lost (**PYLL**) is calculated as follows: For each individual who dies of the cancer of interest, the number of years of expected additional life for an average person of that age, race, and sex is obtained from life tables for the US population (available from the NCHS). The PYLL in the general population associated with a particular cancer for a given year is simply the sum of this expectation over all those individuals who died of that cancer in that year.

Average years of life lost: The average years of life lost (**AYLL**) associated with a particular cancer for a given year is the PYLL associated with that cancer in the general population divided by the number of deaths from that cancer in the general population in that year.

Prevalence: Prevalence is defined as the number or percent of people alive on a certain date in a population who previously had a diagnosis of the disease. It includes new (incident) and pre-existing cases and is a function of past incidence, past survival, and the size and age structure of the population. *Limited-Duration Prevalence* represents the proportion of people alive on a certain day who had a diagnosis of the disease within the past x years (e.g. x = 5, 10,

or 20 years). *Complete prevalence* is an estimate of the number of persons (or the proportion of the population) alive on a specified date who had been diagnosed with the given disease, no matter how long ago that diagnosis was. For more details on cancer prevalence definitions and methods, refer to *http://srab.cancer.gov/prevalence/.*

Stage of disease at diagnosis: Extent-of-disease information determines stage of disease at diagnosis. The **SEER historic stage** presented has four levels. An invasive neoplasm confined entirely to the organ of origin is said to be **localized**. A neoplasm that has extended beyond the limits of the organ of origin, either directly into surrounding organs or tissues or into regional lymph nodes, is said to be **regional**. A neoplasm that has spread to parts of the body remote from the primary tumor, either by direct extension or by discontinuous metastasis, is said to be **distant**. When information is not sufficient to assign a stage, a neoplasm is said to be **unstaged**. In situ tumors (except those of the cervix uteri) are also collected by SEER but generally are not published in this series. For some cancers and diagnosis years, the extent of disease information can also be converted to Stages 0-IV as defined by the American Joint Committee on Cancer (Beahrs et al., 1988).

O-16. REFERENCES

American Cancer Society. Cancer Facts and Figures 2007. Atlanta: American Cancer Society; 2007.

Baquet CR, Horm JW, Gibbs T, Greenwald P. Socioeconomic factors and cancer incidence among blacks and whites. J Natl Cancer Inst 1991; 83:551-557.

Beahrs OH, Henson DE, Hutter RV, Myers MH, editors. Manual for Staging of Cancer, 3rd ed. Philadelphia (PA): Lippincott; 1988.

Breslow L (Chairman, Extramural Committee to Assess Measures of Progress Against Cancer). Measurement of progress against cancer: Final report to the Senate Appropriations Committee. Bethesda: National Cancer Institute; 1988.

Brookmeyer R, Damiano A. Statistical methods for short-term projections of AIDS incidence. Statistics in Medicine 1989;8:23-34.

Byrne J, Kessler LG, Devesa SS. The prevalence of cancer among adults in the United States: 1987. Cancer 1992;68:2154-9.

Capocaccia R, De Angelis R. Estimating the completeness of prevalence based on cancer registry data. Statistics in Medicine 1997;16:425-40.

Clegg LX, Feuer EJ, Midthune D, Fay MP, Hankey BF. Impact of reporting delay and reporting error on cancer incidence rates and trends. J Natl Cancer Inst 2002;94:1537-1545.

Clegg LX, Mitchell GH, Feuer EJ. Estimating the variance of disease prevalence estimates from population-based registries. Technical report 2001. For a copy contact prevalence@ims.nci.nih.gov.

Day, Jennifer Cheeseman, *Population Projections of the United States by Age, Sex, Race, and Hispanic Origin: 1995 to 2050*, U.S. Bureau of the Census, Current Population Reports, P25-1130, U.S. Government Printing Office, Washington, DC, 1996. (*http://www.census.gov/prod/1/pop/p25-1130/p251130.pdf*)

Ederer F, Axtell LM, Cutler SJ. The relative survival rate: A statistical methodology. J Natl Cancer Inst Monogr 1961;6:101-121.

Elandt-Johnson RC, Johnson NL. Survival Models and Data Analysis. New York (NY): Wiley; 1980.

Fay MP. Estimating age conditional probability of developing disease from surveillance data. Popul Health Metr 2004 Jul 27;2(1):6. [http://www.pophealthmetrics.com/content/2/1/6]

Fay MP, Pfeiffer R, Cronin KA, Le C, Feuer EJ. Age-conditional probabilities of developing cancer. Stat Med 2003;22(11):1837-48.

Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon: Stage migration and new diagnostic techniques as a source of misleading statistics for survival of cancer. New Engl J Med 1985;312:1604-1608.

Feldman AR, Kessler L, Myers M, Naughton MD. The prevalence of cancer: Estimates based on the Connecticut Tumor Registry. New Engl J Med 1986; 315:1394-1397.

Feuer EJ, Wun L-M, Boring CC. Probability of developing cancer. In: Miller BA, Ries LAG, Hankey BF, Kosary CL, Edwards BK, editors. Cancer Statistics Review: 1973-1989, National Cancer Institute, NIH Pub. No. 92-2789, 1992. p. XXX.1-8.

Feuer EJ, Wun L-M, Boring CC, Flanders WD, Timmel MJ, Tong T. The lifetime risk of developing breast cancer. J Natl Cancer Inst 1993;85:892-897.

Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, Whelan S, editors. International Classification of Diseases for Oncology, 3rd ed. Geneva: World Health Organization; 2000.

Gail MH, Kessler L, Midthune D, Scoppa S. Two approaches for estimating disease prevalence from population-based registries of incidence and total mortality. Biometrics 1999;55:1137-44.

Hahn RA, Mulinare J, Teutsch SM. Inconsistencies in coding of race and ethnicity between birth and death in U.S. infants. JAMA 1992;267:259-263.

Harris JE. Reporting delays and the incidence of AIDS. Journal of the American Statistical Association 1990;85:915-924.

Ingram DD, Parker JD, Schenker N, Weed JA, Hamilton B, Arias E, Madans JH. United States Census 2000 population with bridged race categories. Vital Health Stat 2. 2003 Sep;(135):1-55.

Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin. 2007 Jan-Feb;57(1):43-66.

Keyfitz N. Sampling variance of standardized mortality rates. Hum Biol 1966;38:309-317.

Kim H-J, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 2000;19:335-351.

Kleinbaum DG, Kupper LL, Muller KE. Applied Regression Analysis and Other Multivariable Methods, 2nd ed. Mariotto A, Gigli A, Capocaccia R, Clegg L, Scoppa S, Ries LA, Tesauro GS, Rowland JS, Feuer EJ. Complete and limited duration prevalence estimates. *SEER Cancer Statistics Review, 1973-1999* 2002;19.

Merrill RM, Feuer EJ, Capocaccia R, Mariotto A. Cancer prevalence estimates based on tumor registry data in the SEER Program. Int J Epidemiol 2000;29:197-207.

Midthune DN, Fay MP, Clegg LX, Feuer EJ. Modeling reporting delays and reporting corrections in cancer registry data. J Am Stat Assoc 2005;100(469):61-70.

Pagano M, Tu XM, De Gruttola V, & MaWhinney S. Regression analysis of censored and truncated data: estimating reporting-delay distributions and AIDS incidence from surveillance data. Biometrics 1994;50:1203-1214.

Percy C, Ries LAG, Van Holten VD. The accuracy of liver cancer as the underlying cause of death on death certificates. Public Health Rep 1990;105:361-368.

Percy C, Van Holten V, Muir C, editors. International Classification of Diseases for Oncology, 2nd ed. Geneva: World Health Organization;1990.

Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg LX, Edwards BK (eds). SEER Cancer Statistics Review, 1973-1997, National Cancer Institute. NIH Pub. No. 00-2789. Bethesda, MD, 2000.

Robinson JG, West KK, Adlakha A. Coverage of the population in Census 2000: Results from demographic analysis. Population Res Policy Rev 2002;21:19-38.

Rosenberg HM, Maurer JD, Sorlie PD, Johnson NJ, MacDorman MF, Hoyert DL, Spitler JF, Scott C. Quality of death rates by race and Hispanic origin: A summary of current research. Hyattsville (MD): National Center for Health Statistics; Vital and Health Statistics, Series 2, No. 128, 1999.

Snedecor GW, Cochran WG. Statistical Methods, 7th ed. Ames (IA): Iowa State University Press; 1980.

US Cancer Statistics Working Group. *United States Cancer Statistics: 1999-2002 Incidence and Mortality Web-based Report Version.* Atlanta: Department of Health and Human Services, Centers for Disease Control and Prevention, *and* National Cancer Institute; 2005. Available at: www.cdc.gov/cancer/npcr/uscs.

US Bureau of the Census. Current Population Reports; Series P-25 No. 985. Washington (DC): US Government Printing Office; 1986.

Zelen M. Theory of early detection of breast cancer in the general population. In: Heuson J-C, Mattheiem WH, Rozencweig M, editors. Breast Cancer: Trends in Research and Treatment. New York (NY): Raven Press; 1976. p. 287-299.

Table IV-1
FEMALE BREAST CANCER (Invasive)

TRENDS IN SEER INCIDENCE[a] AND U.S. MORTALITY[b] USING THE JOINPOINT REGRESSION PROGRAM, 1975-2004
WITH UP TO THREE JOINPOINTS BY RACE AND AGE

		Joinpoint Segment 1		Joinpoint Segment 2		Joinpoint Segment 3		Joinpoint Segment 4	
		Year	APC	Year	APC	Year	APC	Year	APC
SEER Cancer Incidence[a]									
All Races	All Ages	1975-1980	-0.4	1980-1987	3.7*	1987-2001	0.4*	2001-2004	-3.9*
All Races	Under 50	1975-1980	-1.4	1980-1986	2.9*	1986-2004	-0.3*		
All Races	50 and Over	1975-1982	0.8	1982-1986	5.8*	1986-2001	0.7*	2001-2004	-5.1*
White	All Ages	1975-1980	-0.3	1980-1987	3.7*	1987-2001	0.5*	2001-2004	-4.1*
White	Under 50	1975-1980	-1.2	1980-1986	2.8*	1986-2004	-0.3*		
White	50 and Over	1975-1980	0.0	1980-1987	4.2*	1987-2001	0.7*	2001-2004	-5.3*
Black	All Ages	1975-1992	2.3*	1992-2004	-0.3				
Black	Under 50	1975-1991	1.5*	1991-2004	-1.0*				
Black	50 and Over	1975-1994	2.4*	1994-2004	-0.4				
SEER Delay-Adjusted Incidence[a]									
All Races	All Ages	1975-1980	-0.4	1980-1987	3.7*	1987-2001	0.5*	2001-2004	-3.5*
All Races	Under 50	1975-1980	-1.4	1980-1986	2.9*	1986-2004	-0.2		
All Races	50 and Over	1975-1982	0.8	1982-1986	5.8*	1986-2001	0.8*	2001-2004	-4.8*
White	All Ages	1975-1980	-0.3	1980-1987	3.7*	1987-2001	0.6*	2001-2004	-3.7*
White	Under 50	1975-1980	-1.2	1980-1986	2.8*	1986-2004	-0.2		
White	50 and Over	1975-1980	0.0	1980-1987	4.2*	1987-2001	0.8*	2001-2004	-4.8*
Black	All Ages	1975-1992	2.3*	1992-2004	-0.1				
Black	Under 50	1975-1992	1.5*	1992-2002	-1.5*	2002-2004	5.6		
Black	50 and Over	1975-1993	2.6*	1993-2004	0.1				
U.S. Cancer Mortality[b]									
All Races	All Ages	1975-1990	0.4*	1990-2004	-2.2*				
All Races	Under 50	1975-1990	-0.4*	1990-2004	-3.3*				
All Races	50 and Over	1975-1990	0.6*	1990-2004	-2.0*				
White	All Ages	1975-1990	0.3*	1990-2004	-2.4*				
White	Under 50	1975-1990	-0.6*	1990-2004	-3.7*				
White	50 and Over	1975-1990	0.5*	1990-2004	-2.1*				
Black	All Ages	1975-1992	1.5*	1992-2004	-1.3*				
Black	Under 50	1975-1988	1.8*	1988-2004	-1.9*				
Black	50 and Over	1975-1993	1.6*	1993-2004	-1.2*				

Joinpoint Regression Program Version 3.0, April 2005, National Cancer Institute. (http://srab.cancer.gov/joinpoint/).

The APC is the Annual Percent Change based on rates age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130).
[a] Trends are from the SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).
[b] Trends are from the NCHS public use data file for the total US.
* The APC is significantly different from zero (p<.05).

Table IV-2
FEMALE BREAST CANCER (*In Situ*)

TRENDS IN SEER INCIDENCE[a] USING THE JOINPOINT REGRESSION PROGRAM, 1975-2004
WITH UP TO THREE JOINPOINTS BY RACE AND AGE

		Joinpoint Segment 1		Joinpoint Segment 2		Joinpoint Segment 3		Joinpoint Segment 4	
		Year	APC	Year	APC	Year	APC	Year	APC
SEER Cancer Incidence[a]									
All Races	All Ages	1975-1982	-0.8	1982-1986	32.2*	1986-2000	6.1*	2000-2004	-1.2
All Races	Under 50	1975-1982	-2.5	1982-1986	29.5*	1986-2004	3.2*		
All Races	50 and Over	1975-1981	-1.8	1981-1987	25.8*	1987-2000	6.9*	2000-2004	-1.6
White	All Ages	1975-1982	-0.7	1982-1986	32.9*	1986-2000	5.9*	2000-2004	-1.1
White	Under 50	1975-1982	-2.7	1982-1986	30.4*	1986-2004	3.1*		
White	50 and Over	1975-1981	-1.3	1981-1987	26.0*	1987-2000	6.7*	2000-2004	-1.4
Black	All Ages	1975-1981	3.0	1981-1988	18.5*	1988-1999	7.6*	1999-2004	-0.4
Black	Under 50	1975-1997	8.0*	1997-2004	-1.4				
Black	50 and Over	1975-1980	-2.0	1980-1988	20.8*	1988-2000	8.1*	2000-2004	-1.8
SEER Delay-Adjusted Incidence[a]									
All Races	All Ages	1975-1982	-0.8	1982-1986	32.2*	1986-2000	6.1*	2000-2004	-1.0
All Races	Under 50	1975-1982	-2.5	1982-1986	29.4*	1986-2004	3.2*		
All Races	50 and Over	1975-1981	-1.9	1981-1987	25.8*	1987-2000	6.9*	2000-2004	-1.4
White	All Ages	1975-1982	-0.7	1982-1986	32.9*	1986-2000	6.0*	2000-2004	-0.8
White	Under 50	1975-1982	-2.7	1982-1986	30.3*	1986-2004	3.2*		
White	50 and Over	1975-1981	-1.3	1981-1987	26.0*	1987-2000	6.7*	2000-2004	-1.2
Black	All Ages	1975-1981	3.0	1981-1988	18.6*	1988-1999	7.6*	1999-2004	-0.2
Black	Under 50	1975-1997	8.0*	1997-2004	-1.3				
Black	50 and Over	1975-1980	-2.0	1980-1988	20.8*	1988-2000	8.1*	2000-2004	-1.6

Joinpoint Regression Program Version 3.0, April 2005, National Cancer Institute. (http://srab.cancer.gov/joinpoint/).

The APC is the Annual Percent Change based on rates age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130).

[a] Trends are from the SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).

* The APC is significantly different from zero (p<.05).

Table IV-3
BREAST CANCER (Invasive)

AGE ADJUSTED SEER INCIDENCE[a] RATES BY YEAR, RACE AND SEX

	All Races			Whites			Blacks		
	Total	Males	Females	Total	Males	Females	Total	Males	Females
AGE-ADJUSTED RATES									
YEAR OF DIAGNOSIS:									
1975	58.1	0.9	105.1	59.5	0.9	107.4	52.2	-	93.7
1976	56.4	1.1	101.9	58.1	1.1	104.8	48.0	-	85.3
1977	56.0	1.0	100.8	57.5	0.9	103.4	49.7	-	87.0
1978	55.8	0.9	100.6	57.5	0.9	103.6	48.3	-	86.1
1979	56.8	1.0	102.1	58.3	0.9	104.8	49.8	-	86.8
1980	56.8	0.9	102.1	58.5	1.0	105.0	50.5	-	89.2
1981	59.3	1.0	106.3	61.2	0.9	109.9	54.4	-	94.2
1982	59.2	1.0	106.4	61.1	0.9	109.9	53.9	-	93.5
1983	61.9	1.0	111.1	63.7	1.1	114.5	58.8	-	103.4
1984	64.4	0.9	115.9	66.5	0.9	119.8	58.1	-	102.0
1985	69.0	1.0	124.1	71.0	1.0	127.8	63.9	-	111.4
1986	70.4	0.9	126.8	72.3	1.0	130.4	66.2	-	114.9
1987	74.8	1.0	134.4	77.8	1.0	140.3	63.0	-	109.3
1988	73.0	1.2	131.2	75.6	1.2	136.3	68.9	2.8	118.6
1989	70.7	1.1	127.1	73.3	1.1	132.3	60.4	-	104.7
1990	73.1	1.1	131.7	75.3	1.1	136.2	68.3	-	118.2
1991	74.0	1.1	133.7	76.6	1.2	138.8	67.3	-	117.3
1992	72.9	1.0	131.8	74.7	1.0	135.6	71.3	-	123.5
1993	71.2	1.1	129.1	73.1	1.0	133.1	68.8	-	119.4
1994	72.0	1.1	130.8	74.2	1.1	135.6	70.3	-	122.0
1995	72.7	1.0	132.4	75.0	0.9	137.4	71.7	-	123.9
1996	73.2	1.3	133.4	75.2	1.3	137.9	71.1	-	123.3
1997	75.3	1.1	137.5	77.5	1.1	142.4	71.7	-	123.9
1998	77.1	1.1	141.0	79.5	1.1	146.4	70.3	-	122.5
1999	76.9	1.0	140.8	79.3	1.0	146.4	72.2	2.2	124.7
2000	74.0	1.2	135.8	77.0	1.2	142.6	67.2	2.9	115.7
2001	74.8	1.2	137.4	77.6	1.2	143.8	65.4	1.5	113.3
2002	72.7	1.2	133.9	75.0	1.1	139.6	69.2	2.1	119.8
2003	67.6	1.3	124.6	69.5	1.3	129.3	69.4	-	120.6
2004	67.3	1.2	124.3	68.7	1.2	128.2	68.6	1.6	119.3
1975-2004	68.6	1.1	124.5	70.6	1.1	128.5	64.3	1.6	111.9

[a] SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta). Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130).

- Statistic not shown. Rate based on less than 16 cases for the time interval.

Table IV-4
BREAST CANCER (Invasive)

AGE-ADJUSTED U.S. DEATH[a] RATES BY YEAR, RACE AND SEX

	All Races			Whites			Blacks		
	Total	Males	Females	Total	Males	Females	Total	Males	Females
AGE-ADJUSTED RATES									
YEAR OF DEATH:									
1975	17.8	0.4	31.4	18.0	0.4	31.8	16.8	0.4	29.5
1976	18.1	0.4	31.8	18.2	0.4	32.2	17.6	0.6	30.5
1977	18.5	0.4	32.5	18.6	0.4	32.7	18.9	0.5	32.8
1978	18.0	0.4	31.7	18.1	0.3	31.9	18.6	0.6	32.1
1979	17.7	0.3	31.2	17.9	0.3	31.5	17.9	0.5	30.8
1980	18.0	0.3	31.7	18.1	0.3	31.9	18.4	0.4	31.7
1981	18.2	0.3	31.9	18.3	0.3	32.1	19.0	0.5	32.6
1982	18.4	0.3	32.2	18.4	0.3	32.3	19.7	0.6	33.7
1983	18.3	0.3	32.1	18.4	0.3	32.2	19.6	0.5	33.5
1984	18.8	0.3	32.9	18.8	0.3	32.9	21.0	0.5	35.9
1985	18.8	0.3	33.0	18.9	0.3	33.1	20.3	0.4	34.9
1986	18.8	0.3	32.9	18.8	0.3	32.9	20.7	0.4	35.4
1987	18.7	0.3	32.7	18.6	0.3	32.6	21.5	0.5	36.7
1988	19.0	0.3	33.2	18.9	0.3	33.1	22.4	0.9	37.8
1989	19.0	0.3	33.2	18.9	0.3	33.2	21.6	0.5	36.6
1990	18.9	0.3	33.1	18.8	0.3	33.0	22.5	0.5	38.0
1991	18.7	0.3	32.7	18.5	0.3	32.4	22.6	0.4	38.3
1992	18.1	0.3	31.6	17.9	0.3	31.4	21.9	0.4	37.1
1993	18.0	0.4	31.4	17.7	0.3	31.1	22.6	0.7	38.0
1994	17.7	0.4	30.9	17.4	0.3	30.6	22.4	0.6	37.7
1995	17.4	0.4	30.6	17.1	0.3	30.1	22.7	0.8	38.2
1996	16.8	0.3	29.5	16.5	0.3	29.0	22.1	0.7	37.1
1997	16.1	0.3	28.2	15.7	0.3	27.6	22.3	0.6	37.4
1998	15.7	0.3	27.5	15.3	0.3	27.0	21.1	0.6	35.5
1999	15.2	0.3	26.6	14.8	0.3	26.0	20.9	0.7	35.2
2000	15.2	0.4	26.6	14.9	0.4	26.2	20.5	0.6	34.4
2001	14.7	0.3	26.0	14.3	0.3	25.4	20.5	0.6	34.5
2002	14.5	0.3	25.6	14.1	0.3	25.0	20.3	0.6	34.1
2003	14.2	0.3	25.2	13.8	0.3	24.6	20.2	0.5	34.1
2004	13.7	0.3	24.4	13.3	0.3	23.8	19.1	0.5	32.3
1975-2004	17.2	0.3	30.2	17.1	0.3	30.1	20.6	0.6	35.1

[a] NCHS public use data file for the total US. Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130).
- Statistic not shown. Rate based on less than 16 cases for the time interval.

Table IV-5
FEMALE BREAST CANCER (Invasive)

AGE-ADJUSTED SEER INCIDENCE[a] RATES BY YEAR, RACE AND AGE

	All Races, Females			White Females			Black Females		
	All	<50	50+	All	<50	50+	All	<50	50+
SEER INCIDENCE RATES									
YEAR OF DIAGNOSIS:									
1975	105.1	40.6	273.9	107.4	40.7	281.8	93.7	42.6	227.5
1976	101.9	40.0	264.0	104.8	40.9	272.2	85.3	37.8	209.8
1977	100.8	39.1	262.4	103.4	39.4	271.0	87.0	37.6	216.4
1978	100.6	38.8	262.3	103.6	39.2	272.0	86.1	40.2	206.1
1979	102.1	38.0	269.9	104.8	38.6	278.0	86.8	37.7	215.3
1980	102.1	37.7	270.7	105.0	38.3	279.8	89.2	37.4	224.9
1981	106.3	39.2	282.0	109.9	40.1	292.5	94.2	38.9	239.3
1982	106.4	40.5	279.0	109.9	41.3	289.8	93.5	37.9	239.0
1983	111.1	40.2	296.8	114.5	40.9	307.2	103.4	41.2	266.0
1984	115.9	42.3	308.5	119.8	43.1	320.8	102.0	44.5	252.4
1985	124.1	44.3	333.1	127.8	44.5	345.9	111.4	45.3	284.4
1986	126.8	44.4	342.4	130.4	45.2	353.5	114.9	45.3	297.0
1987	134.4	45.4	367.5	140.3	46.5	385.8	109.3	43.1	282.7
1988	131.2	44.0	359.7	136.3	45.0	375.3	118.6	42.9	316.6
1989	127.1	43.4	346.4	132.3	44.4	362.3	104.7	42.2	268.5
1990	131.7	45.6	357.2	136.2	45.4	373.9	118.2	48.8	299.7
1991	133.7	47.1	360.3	138.8	47.2	378.7	117.3	50.9	291.0
1992	131.8	43.4	363.5	135.6	43.6	376.6	123.5	46.9	324.1
1993	129.1	42.7	355.1	133.1	43.2	368.4	119.4	45.2	313.6
1994	130.8	42.3	362.5	135.6	42.6	378.8	122.0	47.2	317.8
1995	132.4	43.1	366.3	137.4	43.7	382.9	123.9	45.4	329.4
1996	133.4	43.4	369.1	137.9	43.8	384.3	123.3	43.9	331.1
1997	137.5	43.3	384.0	142.4	44.0	400.0	123.9	43.9	333.6
1998	141.0	45.3	391.4	146.4	45.6	410.2	122.5	46.1	322.7
1999	140.8	43.5	395.6	146.4	44.8	412.7	124.7	43.3	338.0
2000	135.8	43.2	378.3	142.6	43.9	401.2	115.7	44.1	303.2
2001	137.4	43.4	383.4	143.8	44.4	404.2	113.3	39.2	307.4
2002	133.9	42.2	374.1	139.6	42.9	392.8	119.8	39.8	329.4
2003	124.6	42.5	339.6	129.3	43.2	354.5	120.6	42.0	326.4
2004	124.3	43.5	335.7	128.2	43.4	350.2	119.3	44.9	314.3
1975-2004	124.5	42.8	338.4	128.5	43.3	351.5	111.9	43.3	291.5

[a] SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta). Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130).
- Statistic not shown. Rate based on less than 16 cases for the time interval.

Table IV-6
FEMALE BREAST CANCER (Invasive)

AGE-ADJUSTED U.S. DEATH[a] RATES BY YEAR, RACE AND AGE

	All Races, Females			White Females			Black Females		
	All	<50	50+	All	<50	50+	All	<50	50+
U.S. DEATH RATES									
YEAR OF DEATH:									
1975	31.4	9.1	89.9	31.8	9.0	91.4	29.5	10.7	78.8
1976	31.8	8.7	92.2	32.2	8.6	93.8	30.5	10.2	83.5
1977	32.5	8.9	94.3	32.7	8.7	95.3	32.8	10.5	91.1
1978	31.7	8.7	92.1	31.9	8.5	93.3	32.1	11.4	86.5
1979	31.2	8.6	90.5	31.5	8.3	92.1	30.8	11.4	81.8
1980	31.7	8.6	92.2	31.9	8.4	93.6	31.7	10.8	86.3
1981	31.9	8.5	93.3	32.1	8.2	94.8	32.6	11.5	87.7
1982	32.2	8.4	94.4	32.3	8.2	95.5	33.7	11.2	92.8
1983	32.1	8.2	94.7	32.2	7.9	95.8	33.5	11.2	92.1
1984	32.9	8.6	96.6	32.9	8.2	97.5	35.9	12.5	97.2
1985	33.0	8.6	96.9	33.1	8.3	98.1	34.9	12.0	94.6
1986	32.9	8.6	96.3	32.9	8.3	97.5	35.4	12.9	94.6
1987	32.7	8.4	96.1	32.6	8.0	96.9	36.7	12.9	99.0
1988	33.2	8.4	98.2	33.1	8.0	98.8	37.8	12.7	103.4
1989	33.2	8.4	98.2	33.2	8.1	99.2	36.6	12.4	100.0
1990	33.1	8.3	98.1	33.0	8.0	98.5	38.0	12.0	106.1
1991	32.7	8.2	96.9	32.4	7.7	97.2	38.3	12.3	106.3
1992	31.6	7.8	94.2	31.4	7.4	94.5	37.1	12.0	102.7
1993	31.4	7.4	94.2	31.1	7.0	94.2	38.0	11.7	107.1
1994	30.9	7.4	92.6	30.6	6.9	92.5	37.7	11.7	105.9
1995	30.6	7.3	91.5	30.1	6.8	91.1	38.2	11.7	107.5
1996	29.5	6.9	88.5	29.0	6.4	88.3	37.1	11.7	103.6
1997	28.2	6.7	84.5	27.6	6.2	83.6	37.4	11.0	106.6
1998	27.5	6.3	83.1	27.0	5.8	82.5	35.5	10.6	100.7
1999	26.6	5.7	81.2	26.0	5.2	80.4	35.2	10.3	100.5
2000	26.6	5.9	81.0	26.2	5.4	80.6	34.4	9.9	98.3
2001	26.0	5.9	78.7	25.4	5.4	77.9	34.5	9.9	99.1
2002	25.6	5.6	77.8	25.0	5.1	77.1	34.1	10.0	97.2
2003	25.2	5.6	76.5	24.6	5.1	75.6	34.1	9.7	97.9
2004	24.4	5.2	74.6	23.8	4.6	74.0	32.3	9.3	92.4
1975-2004	30.2	7.4	90.0	30.1	7.0	90.4	35.1	11.1	97.7

[a] NCHS public use data file for the total US. Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130).
- Statistic not shown. Rate based on less than 16 cases for the time interval.

Table IV-7
FEMALE BREAST CANCER (*In Situ*)

AGE ADJUSTED SEER INCIDENCE[a] RATES BY YEAR, RACE AND AGE

	All Races, Females			White Females			Black Females		
	All	<50	50+	All	<50	50+	All	<50	50+
SEER INCIDENCE RATES									
YEAR OF DIAGNOSIS:									
1975	5.8	3.8	11.2	5.9	3.8	11.3	3.9	-	8.3
1976	5.3	2.7	12.0	5.4	2.9	11.8	3.3	-	9.4
1977	4.3	2.6	8.7	4.3	2.6	8.9	3.0	-	-
1978	4.4	2.4	9.7	4.6	2.5	9.9	3.3	-	-
1979	4.6	2.8	9.2	4.7	2.9	9.4	4.8	-	9.6
1980	4.9	3.0	9.7	5.0	3.1	10.2	3.7	-	-
1981	5.0	2.6	11.0	4.9	2.5	11.3	4.1	-	8.7
1982	5.3	2.7	12.0	5.3	2.7	12.2	5.6	2.7	12.9
1983	6.1	3.0	14.1	6.2	3.0	14.5	5.4	-	13.2
1984	8.6	4.8	18.7	9.2	5.2	19.6	6.3	2.4	16.8
1985	11.5	5.9	26.2	12.1	6.3	27.4	8.2	3.5	20.6
1986	13.6	6.8	31.6	14.3	7.2	32.8	9.2	5.1	20.0
1987	17.4	7.8	42.4	18.2	8.3	44.3	12.3	5.5	30.1
1988	17.6	8.2	42.2	18.1	8.5	43.2	16.1	7.4	38.9
1989	16.5	7.0	41.4	17.1	7.3	42.7	14.5	5.5	38.1
1990	19.1	8.4	47.2	19.9	8.8	49.2	15.1	5.5	40.0
1991	19.8	8.8	48.6	20.4	8.9	50.8	15.3	7.3	36.3
1992	21.4	9.0	54.0	22.2	9.2	56.2	19.1	6.8	51.2
1993	20.7	8.4	53.1	21.4	8.8	54.2	16.5	6.1	43.9
1994	22.3	8.8	57.8	22.9	9.1	59.2	20.1	7.5	53.3
1995	24.7	9.6	64.1	25.0	9.9	64.6	22.6	6.4	65.2
1996	25.4	9.8	66.1	25.9	9.8	68.1	22.4	7.7	61.0
1997	28.4	11.1	73.6	29.0	11.2	75.4	28.0	11.4	71.4
1998	32.8	12.0	87.3	33.8	12.3	89.9	30.3	10.8	81.5
1999	32.8	12.0	87.2	33.2	12.2	88.0	29.7	10.4	80.2
2000	32.8	11.8	87.9	33.9	12.5	89.9	29.3	8.0	85.1
2001	33.5	11.5	91.2	34.1	12.0	92.0	31.5	8.9	90.7
2002	33.8	11.8	91.6	34.3	12.2	92.2	28.4	8.6	80.5
2003	32.0	11.8	84.9	32.9	12.3	87.1	29.3	9.2	81.9
2004	32.5	12.5	85.1	33.2	12.7	86.9	30.2	9.6	84.0
1975-2004	19.6	8.3	49.2	19.7	8.4	49.3	18.0	6.7	47.4

[a] SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta). Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130).

\- Statistic not shown. Rate based on less than 16 cases for the time interval.

Table IV-8
BREAST CANCER (Invasive)

SEER INCIDENCE[a] AND U.S. DEATH[b] RATES, AGE-ADJUSTED AND AGE-SPECIFIC RATES, BY RACE AND SEX

	All Races			Whites			Blacks		
	Total	Males	Females	Total	Males	Females	Total	Males	Females
SEER INCIDENCE									
AGE AT DIAGNOSIS									
AGE-ADJUSTED RATES, 2000-2004									
All ages	69.6	1.1	127.8	71.5	1.2	132.5	68.0	1.7	118.3
Under 65	43.6	0.5	84.9	44.2	0.4	87.2	44.3	0.8	81.5
65 and over	249.1	5.9	424.4	260.4	6.1	446.0	231.7	8.0	372.9
All ages(IARC world std)[c]	49.2	0.7	92.4	50.5	0.7	95.8	48.3	1.2	85.8
AGE-SPECIFIC RATES, 2000-2004									
<1	-	-	-	-	-	-	-	-	-
1-4	-	-	-	-	-	-	-	-	-
5-9	-	-	-	-	-	-	-	-	-
10-14	-	-	-	-	-	-	-	-	-
15-19	0.1	-	0.2	-	-	-	-	-	-
20-24	0.7	-	1.4	0.7	-	1.4	1.0	-	2.0
25-29	3.8	-	7.7	3.6	-	7.5	5.4	-	10.4
30-34	12.6	0.1	25.5	12.2	-	25.1	16.8	-	32.1
35-39	29.6	0.1	59.5	28.8	-	58.7	34.5	-	65.7
40-44	59.0	0.3	117.4	58.8	0.3	118.6	62.3	-	117.8
45-49	94.9	0.8	186.7	95.4	0.8	190.1	96.4	1.2	180.2
50-54	121.8	1.1	237.3	124.1	1.0	244.6	124.1	2.0	227.9
55-59	159.7	2.2	307.9	163.9	2.1	319.5	155.6	4.4	281.1
60-64	191.6	3.1	363.7	199.3	3.0	381.9	177.3	5.5	315.3
65-69	223.2	4.4	410.9	234.9	4.5	436.5	201.9	6.3	350.8
70-74	242.9	5.2	432.3	253.9	5.5	455.9	227.8	6.0	381.8
75-79	275.8	6.1	464.8	288.9	6.1	488.6	250.9	10.1	399.2
80-84	271.2	7.5	435.2	281.6	7.6	451.8	258.0	-	392.7
85+	247.3	8.7	355.3	256.0	9.1	366.1	242.2	-	335.2
U.S. MORTALITY									
AGE AT DEATH									
AGE-ADJUSTED RATES, 2000-2004									
All ages	14.5	0.3	25.5	14.1	0.3	25.0	20.1	0.6	33.8
Under 65	6.8	0.1	13.1	6.3	0.1	12.4	11.1	0.2	20.2
65 and over	67.6	1.8	111.4	67.6	1.8	112.0	82.3	3.0	127.9
All ages(IARC world std)[c]	9.1	0.2	16.7	8.8	0.2	16.2	13.2	0.3	23.0
AGE-SPECIFIC RATES, 2000-2004									
<1	-	-	-	-	-	-	-	-	-
1-4	-	-	-	-	-	-	-	-	-
5-9	-	-	-	-	-	-	-	-	-
10-14	-	-	-	-	-	-	-	-	-
15-19	-	-	-	-	-	-	-	-	-
20-24	0.1	-	0.1	0.0	-	0.1	0.1	-	0.2
25-29	0.4	-	0.8	0.3	-	0.6	0.9	-	1.7
30-34	1.7	-	3.5	1.5	-	3.0	3.6	-	6.9
35-39	4.2	0.0	8.3	3.7	0.0	7.5	7.9	-	14.8
40-44	7.9	0.1	15.6	7.1	0.0	14.1	14.5	-	27.1
45-49	12.8	0.1	25.1	11.7	0.1	23.1	22.6	0.3	42.0
50-54	19.7	0.3	38.2	18.4	0.3	36.1	32.1	0.6	58.8
55-59	26.8	0.5	51.6	25.6	0.4	49.8	42.1	0.8	76.0
60-64	33.9	0.7	64.0	33.1	0.7	63.0	47.7	1.5	83.9
65-69	41.4	1.0	76.3	41.0	1.0	76.2	54.1	1.6	93.0
70-74	52.6	1.4	93.4	52.4	1.4	94.0	66.1	2.5	108.8
75-79	67.4	2.0	113.6	67.7	1.9	114.8	80.3	2.7	126.8
80-84	87.4	2.5	138.9	87.7	2.4	139.8	104.0	3.7	155.9
85+	134.1	3.6	190.2	134.5	3.5	190.9	156.4	7.1	213.7

[a] SEER 17 areas. Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130), unless noted.
[b] NCHS public use data file for the total US. Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130), unless noted.
[c] Rates are per 100,000 and are age-adjusted to the IARC world standard population.
- Statistic not shown. Rate based on less than 16 cases for the time interval.

Table IV-9
FEMALE BREAST CANCER (*In Situ*)

SEER INCIDENCE[a] RATES, AGE-ADJUSTED AND AGE-SPECIFIC RATES, BY RACE

	All Races, Females	White Females	Black Females
AGE-ADJUSTED RATES, 2000-2004			
AGE AT DIAGNOSIS:			
All ages	29.4	30.2	25.4
Under 65	21.9	22.6	17.6
65 and over	81.3	83.1	79.1
All ages(IARC world std)[b]	22.2	22.8	19.0
AGE-SPECIFIC RATES, 2000-2004			
AGE AT DIAGNOSIS:			
<1	-	-	-
1-4	-	-	-
5-9	-	-	-
10-14	-	-	-
15-19	-	-	-
20-24	0.2	0.2	-
25-29	0.7	0.8	-
30-34	2.4	2.3	3.0
35-39	10.0	10.5	8.4
40-44	33.6	34.9	22.8
45-49	54.1	55.9	39.9
50-54	67.0	68.3	53.0
55-59	80.3	82.6	71.4
60-64	86.7	89.1	74.9
65-69	96.8	99.3	94.2
70-74	92.4	94.9	93.4
75-79	86.5	88.2	84.2
80-84	65.0	66.4	54.0
85+	33.9	33.6	36.7

[a] SEER 17 areas. Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130), unless noted.
[b] Rates are per 100,000 and are age-adjusted to the IARC world standard population.
\- Statistic not shown. Rate based on less than 16 cases for the time interval.

Table IV-10
FEMALE BREAST CANCER (Invasive)
SURVIVAL RATES, BY RACE, DIAGNOSIS YEAR, STAGE AND AGE

	All Races, Females			White Females			Black Females		
	All	<50	50+	All	<50	50+	All	<50	50+
5-YR RELATIVE SURVIVAL RATES									
YEAR OF DIAGNOSIS:									
1960-1963[a]	-	-	-	63	-	-	46	-	-
1970-1973[a]	-	-	-	68	-	-	51	-	-
1975-1977[b]	75.1	76.7	74.6	75.9	77.9	75.2	62.3	62.6	62.2
1978-1980[b]	74.9	75.6	74.7	75.6	76.2	75.4	63.8	66.9	62.0
1981-1983[b]	76.7	77.5	76.5	77.7	78.7	77.4	64.1	65.2	63.4
1984-1986[b]	79.3	77.9	79.8	80.4	79.7	80.6	65.1	63.8	65.8
1987-1989[b]	84.2	81.5	85.2	85.3	82.8	86.1	71.2	69.5	72.1
1990-1992[b]	85.5	83.4	86.3	86.7	85.1	87.3	71.7	70.0	72.8
1993-1995[b]	86.6	84.3	87.5	87.9	86.3	88.5	72.8	70.0	74.6
1996-2003[b]	89.2[e]	87.3[e]	89.9[e]	90.3[e]	89.0[e]	90.7[e]	77.9[e]	76.0[e]	79.1[e]
5-YR PERIOD SURVIVAL RATES[cd]									
YEAR OF DIAGNOSIS:									
1996-2003	89.1	87.3	89.8	90.2	88.6	90.7	78.3	76.8	79.2
STAGE DISTRIBUTION (%) 1996-2003[c]									
All Stages									
Number of cases	253,801	63,159	190,642	211,686	48,951	162,735	22,307	7,442	14,865
Percent	100%	100%	100%	100%	100%	100%	100%	100%	100%
Localized	61	54	63	62	54	64	51	46	54
Regional	31	39	28	30	39	28	37	43	33
Distant	6	5	6	6	5	6	9	9	10
Unstaged	2	2	2	2	1	2	3	2	3
5-YR RELATIVE SURVIVAL RATES, 1996-2003[c]									
AGE AT DIAGNOSIS:									
<45	84.9	-	-	86.6	-	-	72.5	-	-
45-54	88.9	-	-	90.1	-	-	78.4	-	-
55-64	89.8	-	-	91.0	-	-	78.6	-	-
65-74	90.4	-	-	91.1	-	-	80.1	-	-
75+	88.4	-	-	89.0	-	-	78.5	-	-
Under 65	88.3	-	-	89.7	-	-	76.6	-	-
65 and over	89.6	-	-	90.3	-	-	79.4	-	-
STAGE:									
All Stages	88.6	86.7	89.4	89.7	88.2	90.3	77.3	75.1	78.5
Localized	98.0	95.4	98.9	98.5	95.8	99.3	93.2	90.5	94.6
Regional	83.5	82.7	84.0	84.9	84.5	85.1	72.4	71.6	73.0
Distant	26.7	33.5	24.4	28.3	37.9	25.4	17.4	17.4	17.3
Unstaged	56.9	70.0	52.8	57.6	74.1	53.1	46.1	50.2	43.8
IN SITU[h]	100.0	100.0	100.0	100.0	100.0	100.0	100.0	99.2	100.0

[a] Rates are based on End Results data from a series of hospital registries and one population-based registry.
[b] Rates are from the SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta).
Rates are based on follow-up of patients into 2004.
[c] Rates are from the SEER 17 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana and New Jersey). California excluding SF/SJM/LA, Kentucky, Louisiana, and New Jersey contribute cases for diagnosis years 2000-2003. The remaining 13 SEER Areas contribute cases for the entire period 1996-2003. Rates are based on follow-up of patients into 2004.
[d] Period survival provides a more up-to-date estimate of survival by piecing together the most recent conditional survival estimates from several cohorts. It is computed here using three calendar year blocks (2001-2003: 0-1 year survival), (2000-2002: 1-2 year survival), (1999-2001: 2-3 year survival), (1998-2000: 3-4 year survival), (1997-1999: 4-5 years survival).
[e] The difference in rates between 1975-1977 and 1996-2003 is statistically significant ($p<.05$).
[f] The standard error of the survival rate is between 5 and 10 percentage points.
[g] The standard error of the survival rate is greater than 10 percentage points.
[h] *In situ* cases are not included in the All Stages group.
- Statistic could not be calculated due to fewer than 16 cases during the time period.

Table IV-11
FEMALE BREAST CANCER (Invasive)

SURVIVAL RATES[a]

By Year of Diagnosis

All Races, Females

Year of Diagnosis

	1975-1979	1980-1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
Relative Survival Rates (SEER[b])																					
1-year	94.7	95.5	95.8	96.3	96.9	96.8	97.0	97.0	97.4	97.4	97.2	97.6	97.3	97.2	97.6	97.7	97.6	97.7	97.5	97.7	98.0
2-year	88.9	90.5	91.2	91.7	93.3	93.4	93.3	93.4	93.9	94.5	94.1	94.4	94.2	94.0	94.6	95.1	95.3	95.6	95.3	95.7	
3-year	83.4	85.1	86.3	87.0	89.3	90.1	90.0	89.8	90.3	91.2	91.0	91.2	91.5	91.1	92.2	93.2	93.3	93.7	93.0		
4-year	78.7	80.7	82.3	83.5	86.1	87.3	87.1	87.0	87.8	88.3	88.3	88.8	89.0	89.2	90.1	91.3	91.4	91.8			
5-year	74.9	76.9	78.8	80.5	83.3	84.7	84.6	84.8	85.5	86.1	86.0	86.8	86.9	86.9	88.6	89.7	89.7				
6-year	71.8	73.9	76.3	78.2	80.7	82.5	82.3	82.7	83.6	84.3	84.0	85.2	85.6	85.2	87.1	88.5					
7-year	69.1	71.1	74.1	75.9	78.5	80.7	80.6	80.8	81.8	82.6	82.3	83.8	83.9	84.1	86.0						
8-year	66.9	68.8	72.3	74.4	77.0	79.2	79.2	79.5	80.3	81.7	80.8	83.0	82.7	82.7							
9-year	64.7	66.9	70.4	72.8	75.2	77.5	77.9	78.1	78.9	80.7	79.7	81.8	81.4								
10-year	62.9	65.0	68.7	71.1	73.9	76.5	76.7	77.0	77.9	79.8	78.7	80.6									
11-year	61.3	63.2	67.3	70.0	72.3	75.4	75.8	75.9	77.1	78.7	77.4										
12-year	59.7	62.0	66.2	68.6	71.0	74.3	74.3	75.0	75.9	77.7											
13-year	58.6	61.0	65.3	67.6	69.8	73.2	73.5	73.9	75.0												
14-year	57.6	59.7	64.6	66.7	68.6	72.6	72.5	72.8													
15-year	56.6	58.9	63.6	65.3	67.9	71.7	71.6														
16-year	55.7	57.8	62.5	64.4	66.7	71.1															
17-year	54.8	56.9	61.3	63.8	66.3																
18-year	54.1	56.2	60.4	63.3																	
19-year	53.3	55.6	60.1																		
20-year	52.7	54.9																			

[a] Survival rates are relative rates expressed as percents.
[b] Rates are from the SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).

Table IV-12
FEMALE BREAST CANCER (Under 50) (Invasive)

SURVIVAL RATES[a]

By Year of Diagnosis

All Races, Females

Year of Diagnosis

	1975-1979	1980-1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
Relative Survival Rates (SEER[b])																					
1-year	96.8	97.6	97.6	98.0	98.0	98.4	98.1	97.6	98.5	98.4	98.0	98.4	98.0	97.8	98.1	98.4	98.6	98.5	98.4	98.6	98.9
2-year	90.9	91.5	91.9	92.3	92.7	93.8	93.1	93.1	93.9	94.6	94.3	93.6	93.7	93.8	94.7	95.2	95.1	95.7	94.8	95.7	
3-year	84.7	85.7	85.8	86.1	87.3	89.2	88.7	88.5	90.0	90.8	90.2	89.3	90.0	90.7	91.7	92.3	92.2	93.1	91.5		
4-year	80.1	81.1	81.2	82.1	83.2	85.6	84.9	85.0	86.8	86.5	87.1	86.2	86.7	88.2	88.8	89.5	90.0	90.4			
5-year	76.2	77.2	77.9	78.4	79.9	82.4	82.1	82.4	83.9	83.8	84.7	84.0	84.2	85.5	86.8	87.4	88.0				
6-year	73.4	74.2	75.6	75.9	77.4	80.4	79.7	80.1	81.7	81.7	82.9	81.9	82.3	83.2	84.7	85.4					
7-year	70.9	71.6	73.5	73.2	75.1	78.4	78.0	78.5	79.5	80.2	81.1	80.2	80.2	81.6	83.2						
8-year	68.9	69.5	71.8	71.5	73.6	76.7	76.6	76.6	78.0	78.6	79.5	78.9	78.6	79.9							
9-year	67.0	67.7	69.9	70.4	71.7	75.3	74.9	75.4	77.1	77.6	78.4	77.4	77.4								
10-year	65.5	66.3	68.7	69.3	70.2	73.9	74.2	74.2	76.2	76.7	77.2	76.4									
11-year	64.2	65.0	67.9	68.3	68.7	72.9	73.1	73.3	75.1	75.7	76.5										
12-year	62.8	64.0	66.7	67.1	67.3	72.4	72.0	72.4	73.7	75.0											
13-year	61.7	62.9	65.7	66.0	66.4	71.3	70.9	71.2	72.9												
14-year	60.9	61.8	65.0	65.3	65.5	70.8	70.2	70.7													
15-year	60.2	61.0	64.1	64.5	64.9	70.0	69.4														
16-year	59.4	60.3	63.3	63.9	64.2	69.3															
17-year	58.9	59.6	62.3	63.2	63.8																
18-year	58.3	58.9	61.5	62.6																	
19-year	57.6	58.5	61.0																		
20-year	56.9	57.9																			

[a] Survival rates are relative rates expressed as percents.
[b] Rates are from the SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).

Table IV-13
FEMALE BREAST CANCER (50 and Over) (Invasive)

SURVIVAL RATES[a]

By Year of Diagnosis

All Races, Females

Year of Diagnosis

	1975-1979	1980-1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
Relative Survival Rates (SEER[b])																					
1-year	94.0	94.9	95.3	95.8	96.5	96.3	96.6	96.8	97.0	97.1	96.9	97.3	97.1	97.0	97.4	97.5	97.3	97.4	97.3	97.4	97.6
2-year	88.3	90.1	91.0	91.5	93.5	93.3	93.4	93.5	93.9	94.4	94.1	94.7	94.3	94.0	94.5	95.1	95.4	95.6	95.5	95.7	
3-year	83.0	84.9	86.5	87.3	89.9	90.3	90.4	90.3	90.3	91.3	91.3	91.8	92.1	91.3	92.4	93.5	93.7	93.9	93.5		
4-year	78.2	80.6	82.6	84.0	87.0	87.8	87.9	87.7	88.1	89.0	88.7	89.7	89.9	89.6	90.6	91.9	92.0	92.4			
5-year	74.4	76.8	79.1	81.2	84.5	85.5	85.6	85.8	86.1	86.9	86.5	87.9	88.0	87.5	89.2	90.6	90.4				
6-year	71.2	73.8	76.5	79.1	81.8	83.3	83.3	83.7	84.4	85.3	84.5	86.6	86.9	86.1	88.1	89.8					
7-year	68.4	71.0	74.4	76.9	79.7	81.5	81.6	81.7	82.9	83.6	82.9	85.2	85.5	85.2	87.2						
8-year	66.1	68.6	72.5	75.5	78.4	80.2	80.3	80.7	81.3	83.1	81.4	84.7	84.5	84.0							
9-year	63.8	66.6	70.6	73.7	76.6	78.5	79.2	79.3	79.8	82.2	80.4	83.7	83.3								
10-year	61.9	64.5	68.7	71.9	75.5	77.7	77.9	78.3	78.7	81.2	79.5	82.5									
11-year	60.1	62.5	67.1	70.8	73.8	76.5	77.1	77.3	78.2	80.2	77.9										
12-year	58.4	61.3	66.0	69.4	72.8	75.2	75.6	76.4	77.1	79.1											
13-year	57.2	60.2	65.2	68.4	71.5	74.2	74.9	75.4	76.3												
14-year	56.1	58.8	64.5	67.5	70.2	73.5	73.9	74.2													
15-year	54.8	57.9	63.4	65.9	69.5	72.7	73.0														
16-year	53.8	56.7	62.2	64.9	68.3	72.2															
17-year	52.7	55.6	60.8	64.4	67.9																
18-year	51.8	54.8	59.8	63.9																	
19-year	50.9	54.1	59.5																		
20-year	50.2	53.3																			

[a] Survival rates are relative rates expressed as percents.
[b] Rates are from the SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).

Table IV-14
FEMALE BREAST CANCER (Invasive)

Risk of Being Diagnosed With Cancer in 10, 20 and 30 Years, Lifetime Risk of Being Diagnosed with Cancer, and Lifetime Risk of Dying from Cancer Given Cancer Free At Current Age
2002-2004 By Race/Ethnicity

Race/ Ethnicity	Current Age	Risk of Being Diagnosed with Cancer +10 yrs Percent (95% C.I.)	+20 yrs Percent (95% C.I.)	+30 yrs Percent (95% C.I.)	Eventually Percent (95% C.I.)	Risk of Dying from Cancer Eventually Percent (95% C.I.)
All Races	0	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.06 (0.05, 0.06)	12.28 (12.22, 12.35)	2.89 (2.88, 2.91)
	10	0.00 (0.00, 0.00)	0.06 (0.05, 0.06)	0.48 (0.47, 0.49)	12.42 (12.36, 12.49)	2.93 (2.91, 2.95)
	20	0.05 (0.05, 0.06)	0.48 (0.47, 0.49)	1.89 (1.87, 1.91)	12.45 (12.38, 12.52)	2.94 (2.92, 2.95)
	30	0.43 (0.42, 0.44)	1.84 (1.82, 1.86)	4.24 (4.21, 4.27)	12.46 (12.40, 12.53)	2.95 (2.93, 2.96)
	40	1.43 (1.42, 1.45)	3.86 (3.83, 3.89)	7.04 (6.99, 7.08)	12.19 (12.12, 12.26)	2.92 (2.90, 2.93)
	50	2.51 (2.49, 2.54)	5.79 (5.75, 5.84)	8.93 (8.87, 8.98)	11.12 (11.05, 11.19)	2.78 (2.76, 2.79)
	60	3.51 (3.48, 3.55)	6.87 (6.81, 6.92)	8.76 (8.70, 8.83)	9.21 (9.15, 9.28)	2.47 (2.45, 2.48)
	70	3.88 (3.83, 3.92)	6.07 (6.01, 6.13)	- (- , -)	6.59 (6.53, 6.65)	2.04 (2.02, 2.06)
	80	3.04 (3.00, 3.09)	- (- , -)	- (- , -)	3.76 (3.71, 3.81)	1.55 (1.53, 1.57)
White	0	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.05 (0.05, 0.06)	12.80 (12.72, 12.87)	2.89 (2.87, 2.90)
	10	0.00 (0.00, 0.00)	0.05 (0.05, 0.06)	0.48 (0.47, 0.49)	12.92 (12.84, 13.00)	2.92 (2.90, 2.93)
	20	0.05 (0.05, 0.06)	0.48 (0.47, 0.49)	1.91 (1.88, 1.93)	12.95 (12.87, 13.03)	2.92 (2.91, 2.94)
	30	0.43 (0.42, 0.44)	1.86 (1.84, 1.88)	4.34 (4.30, 4.37)	12.96 (12.89, 13.04)	2.93 (2.92, 2.95)
	40	1.45 (1.43, 1.47)	3.96 (3.92, 3.99)	7.31 (7.25, 7.36)	12.69 (12.61, 12.76)	2.91 (2.89, 2.92)
	50	2.59 (2.56, 2.61)	6.04 (5.99, 6.09)	9.35 (9.28, 9.42)	11.60 (11.52, 11.68)	2.78 (2.76, 2.80)
	60	3.69 (3.65, 3.73)	7.22 (7.16, 7.29)	9.19 (9.12, 9.26)	9.63 (9.55, 9.70)	2.48 (2.46, 2.50)
	70	4.08 (4.03, 4.13)	6.35 (6.29, 6.41)	- (- , -)	6.86 (6.79, 6.93)	2.05 (2.03, 2.07)
	80	3.16 (3.11, 3.21)	- (- , -)	- (- , -)	3.87 (3.81, 3.93)	1.55 (1.53, 1.57)
Black	0	0.00 (0.00, 0.00)	0.00 (0.00, 0.01)	0.07 (0.06, 0.08)	10.10 (9.91, 10.29)	3.23 (3.18, 3.28)
	10	0.00 (0.00, 0.01)	0.07 (0.06, 0.08)	0.53 (0.50, 0.56)	10.32 (10.13, 10.52)	3.30 (3.25, 3.35)
	20	0.07 (0.06, 0.08)	0.53 (0.50, 0.56)	1.87 (1.82, 1.93)	10.35 (10.15, 10.55)	3.31 (3.26, 3.37)
	30	0.46 (0.44, 0.49)	1.82 (1.76, 1.87)	4.04 (3.95, 4.13)	10.37 (10.17, 10.57)	3.33 (3.27, 3.38)
	40	1.38 (1.34, 1.43)	3.65 (3.56, 3.73)	6.24 (6.11, 6.38)	10.11 (9.91, 10.31)	3.27 (3.22, 3.33)
	50	2.38 (2.31, 2.46)	5.12 (5.00, 5.25)	7.52 (7.36, 7.70)	9.19 (8.99, 9.40)	3.06 (3.00, 3.11)
	60	3.04 (2.93, 3.14)	5.70 (5.54, 5.87)	7.14 (6.95, 7.33)	7.55 (7.35, 7.76)	2.64 (2.58, 2.69)
	70	3.26 (3.13, 3.39)	5.01 (4.84, 5.20)	- (- , -)	5.52 (5.32, 5.72)	2.17 (2.11, 2.23)
	80	2.66 (2.51, 2.82)	- (- , -)	- (- , -)	3.43 (3.23, 3.63)	1.74 (1.68, 1.81)

Source: Devcan Version 6.2.0, April 2006, National Cancer Institute (http://srab.cancer.gov/devcan/).
Incidence data are from the SEER 17 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana and New Jersey).
Mortality data are from the NCHS public use data file for the total US.
- Statistic could not be calculated.
A percent or confidence interval value of 0.00 represents a value that is below 0.005.

Table IV-14 - continued
FEMALE BREAST CANCER (Invasive)

Risk of Being Diagnosed With Cancer in 10, 20 and 30 Years, Lifetime Risk of Being Diagnosed with Cancer, and Lifetime Risk of Dying from Cancer Given Cancer Free At Current Age
2002-2004 By Race/Ethnicity

Race/ Ethnicity	Current Age	Risk of Being Diagnosed with Cancer: +10 yrs Percent (95% C.I.)	+20 yrs Percent (95% C.I.)	+30 yrs Percent (95% C.I.)	Eventually Percent (95% C.I.)	Risk of Dying from Cancer: Eventually Percent (95% C.I.)
Asian/ Pacific Islander	0	0.00 (0.00, 0.00)	0.00 (0.00, 0.01)	0.04 (0.04, 0.05)	9.18 (8.95, 9.43)	1.74 (1.63, 1.87)
	10	0.00 (0.00, 0.00)	0.05 (0.04, 0.05)	0.44 (0.41, 0.47)	9.26 (9.02, 9.51)	1.76 (1.64, 1.89)
	20	0.04 (0.04, 0.05)	0.44 (0.41, 0.47)	1.74 (1.68, 1.80)	9.27 (9.04, 9.52)	1.76 (1.64, 1.89)
	30	0.40 (0.37, 0.42)	1.70 (1.64, 1.76)	3.62 (3.52, 3.71)	9.26 (9.02, 9.51)	1.76 (1.64, 1.89)
	40	1.31 (1.27, 1.36)	3.24 (3.16, 3.33)	5.47 (5.34, 5.61)	8.93 (8.69, 9.18)	1.73 (1.62, 1.87)
	50	1.97 (1.90, 2.04)	4.25 (4.12, 4.37)	6.27 (6.11, 6.44)	7.78 (7.55, 8.03)	1.61 (1.50, 1.75)
	60	2.37 (2.28, 2.47)	4.49 (4.34, 4.64)	5.70 (5.51, 5.90)	6.07 (5.84, 6.31)	1.37 (1.25, 1.50)
	70	2.30 (2.19, 2.41)	3.62 (3.45, 3.80)	- (- , -)	4.01 (3.80, 4.25)	1.08 (0.96, 1.22)
	80	1.61 (1.47, 1.75)	- (- , -)	- (- , -)	2.09 (1.88, 2.33)	0.81 (0.68, 0.97)
American Indian/ Alaska Native[a]	0	0.00 (0.00, 0.04)	0.00 (0.00, 0.04)	0.03 (0.01, 0.09)	6.49 (5.81, 7.40)	1.94 (1.69, 2.26)
	10	0.00 (0.00, 0.02)	0.03 (0.01, 0.07)	0.25 (0.18, 0.34)	6.58 (5.89, 7.50)	1.97 (1.71, 2.29)
	20	0.03 (0.01, 0.07)	0.25 (0.18, 0.34)	1.08 (0.92, 1.25)	6.61 (5.92, 7.54)	1.98 (1.72, 2.30)
	30	0.22 (0.16, 0.31)	1.05 (0.90, 1.23)	2.50 (2.23, 2.81)	6.64 (5.94, 7.58)	1.99 (1.73, 2.32)
	40	0.85 (0.71, 1.00)	2.32 (2.05, 2.62)	3.97 (3.55, 4.44)	6.55 (5.84, 7.49)	1.98 (1.72, 2.32)
	50	1.53 (1.31, 1.78)	3.24 (2.84, 3.69)	4.84 (4.27, 5.46)	5.91 (5.20, 6.88)	1.93 (1.66, 2.27)
	60	1.83 (1.51, 2.20)	3.54 (3.01, 4.14)	4.54 (3.87, 5.31)	4.69 (3.99, 5.68)	1.74 (1.46, 2.10)
	70	1.99 (1.55, 2.51)	3.15 (2.51, 3.92)	- (- , -)	3.33 (2.65, 4.37)	1.56 (1.25, 1.96)
	80	1.58 (1.05, 2.30)	- (- , -)	- (- , -)	1.82 (1.20, 2.99)	1.42 (1.06, 1.93)
Hispanic[b]	0	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.05 (0.04, 0.05)	9.23 (9.01, 9.46)	2.08 (2.01, 2.16)
	10	0.00 (0.00, 0.00)	0.05 (0.04, 0.05)	0.37 (0.35, 0.39)	9.32 (9.10, 9.55)	2.10 (2.03, 2.18)
	20	0.04 (0.04, 0.05)	0.37 (0.35, 0.39)	1.45 (1.41, 1.49)	9.34 (9.12, 9.57)	2.11 (2.03, 2.19)
	30	0.33 (0.31, 0.34)	1.41 (1.37, 1.45)	3.19 (3.11, 3.26)	9.33 (9.11, 9.57)	2.11 (2.04, 2.19)
	40	1.09 (1.06, 1.13)	2.89 (2.82, 2.96)	5.10 (4.98, 5.21)	9.09 (8.86, 9.32)	2.08 (2.01, 2.16)
	50	1.84 (1.78, 1.90)	4.10 (3.99, 4.21)	6.30 (6.14, 6.45)	8.19 (7.97, 8.43)	1.97 (1.89, 2.05)
	60	2.38 (2.29, 2.47)	4.69 (4.55, 4.83)	6.07 (5.89, 6.26)	6.68 (6.46, 6.92)	1.73 (1.66, 1.81)
	70	2.57 (2.46, 2.69)	4.11 (3.94, 4.28)	- (- , -)	4.79 (4.57, 5.03)	1.42 (1.34, 1.51)
	80	1.98 (1.84, 2.13)	- (- , -)	- (- , -)	2.85 (2.62, 3.11)	1.12 (1.03, 1.22)

Devcan Version 6.2.0, April 2006, National Cancer Institute (http://srab.cancer.gov/devcan/).
Source: Incidence data are from the SEER 17 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana and New Jersey). Mortality data are from the NCHS public use data file for the total US.

[a] Underlying incidence and mortlaity data for American Indian/Alaska Native are based on the CHSDA(Contract Health Service Delivery Area) counties.

[b] Hispanic is not mutually exclusive from whites, blacks, Asian/Pacific Islanders, and American Indians/Alaska Natives. Underlying incidence data for Hispanics are based on NHIA and exclude cases from the Alaska Native Registry and Kentucky. Underlying mortality data for Hispanics exclude deaths from Minnesota, New Hampshire and North Dakota.

- Statistic could not be calculated.

A percent or confidence interval value of 0.00 represents a value that is below 0.005.

Table IV-15
FEMALE BREAST CANCER (Invasive)

SEER INCIDENCE AND U.S. MORTALITY
AGE-ADJUSTED RATES AND TRENDS[a]
By Race/Ethnicity

SEER Incidence

RACE/ETHNICITY	Rate 2000-2004[b] Rate per 100,000 persons Females	Trend 1995-2004[c] APC (%) Females
All Races	127.8	-1.0
White	132.5	-0.9
White Hispanic[d]	91.2	-0.8
White Non-Hispanic[d]	140.2	-0.8
Black	118.3	-0.5*
Asian/Pacific Islander	89.0	0.0
Amer Ind/Alaska Nat[e]	69.8	-1.9
Hispanic[d]	89.3	-0.7

U.S. Mortality[f]

RACE/ETHNICITY	Rate 2000-2004 Rate per 100,000 persons Females	Trend 1995-2004 APC (%) Females
All Races	25.5	-2.3*
White	25.0	-2.4*
White Hispanic[d]	16.7	-2.3*
White Non-Hispanic[d]	25.5	-2.3*
Black	33.8	-1.6*
Asian/Pacific Islander	12.6	-0.3
Amer Ind/Alaska Nat		
Total U.S.	13.9	-1.2
CHSDA Counties	16.1	0.2
Non-CHSDA Counties	11.2	-3.2
Hispanic[d]	16.1	-2.4*

The APC is the Annual Percent Change over the time interval.

~ Statistic not shown. Rate based on less than 16 cases for the time interval. Trend based on less than 10 cases for at least one year within the time interval.

a Rates are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Trends are based on rates age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130).

b Incidence data used in calculating the rates are from the 17 SEER areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana and New Jersey).

c Incidence data used in calculating the trends are from the 13 SEER areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry and Rural Georgia).

d Hispanic and Non-Hispanic are not mutually exclusive from whites, blacks, Asian/Pacific Islanders, and American Indians/Alaska Natives. Incidence data for Hispanics and Non-Hispanics are based on NHIA and exclude cases from the Alaska Native Registry and Kentucky. The 2000-2004 Hispanic and Non-Hispanic death rates exclude deaths from Minnesota, New Hampshire and North Dakota. The 1995-2004 Hispanic and Non-Hispanic mortality trends exclude deaths from Maine, Minnesota, New Hampshire, North Dakota, and Oklahoma.

e Incidence data for American Indian/Alaska Native are based on the CHSDA(Contract Health Service Delivery Area) counties.

f Mortality data are analyzed from a public use file provided by the National Center for Health Statistics (NCHS).

* The APC is significantly different from zero ($p<.05$).

Table IV-16
FEMALE BREAST CANCER (*In Situ*)

SEER INCIDENCE
AGE-ADJUSTED RATES AND TRENDS[a]
By Race/Ethnicity

RACE/ETHNICITY	Rate 2000-2004[b] Rate per 100,000 persons Females	Trend 1995-2004[c] APC (%) Females
All Races	29.4	2.6*
White	30.2	2.5*
White Hispanic[d]	18.3	3.2*
White Non-Hispanic[d]	33.0	2.7*
Black	25.4	2.7*
Asian/Pacific Islander	25.3	4.5*
Amer Ind/Alaska Nat[e]	15.5	1.8
Hispanic[d]	17.9	3.1*

The APC is the Annual Percent Change over the time interval.

\- Statistic not shown. Rate based on less than 16 cases for the time interval. Trend based on less than 10 cases for at least one year within the time interval.

a Rates are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Trends are based on rates age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130).

b Incidence data used in calculating the rates are from the 17 SEER areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana and New Jersey).

c Incidence data used in calculating the trends are from the 13 SEER areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry and Rural Georgia).

d Hispanic and Non-Hispanic are not mutually exclusive from whites, blacks, Asian/Pacific Islanders, and American Indians/Alaska Natives. Incidence data for Hispanics and Non-Hispanics are based on NHIA and exclude cases from the Alaska Native Registry and Kentucky.

e Incidence data for American Indian/Alaska Native are based on the CHSDA(Contract Health Service Delivery Area) counties.

* The APC is significantly different from zero ($p<.05$).

Table IV-17
FEMALE BREAST CANCER (Invasive)

AGE-ADJUSTED SEER INCIDENCE RATES[a]
By Registry, Race/Ethnicity and Age

	All Races			Whites			Blacks		
	All Ages	Ages <50	Ages 50+	All Ages	Ages <50	Ages 50+	All Ages	Ages <50	Ages 50+
SEER INCIDENCE RATES[a], 2000-2004									
REGISTRY									
Atlanta & Rural Georgia	128.9	43.1	353.6	137.0	43.8	381.2	116.9	43.2	309.7
Atlanta	130.1	43.2	357.7	138.2	43.8	385.6	118.2	43.4	314.2
Rural Georgia	110.8	42.9	288.7	115.7	45.4	299.8	103.4	40.5	268.1
California	126.5	40.0	353.0	133.1	40.5	375.8	118.4	41.1	320.7
Greater Bay Area	129.7	42.6	357.9	142.6	43.6	401.7	116.2	42.0	310.4
San Francisco-Oakland	132.3	43.3	365.3	146.6	44.5	413.8	119.1	42.6	319.3
San Jose-Monterey	124.8	41.4	343.3	135.5	42.0	380.6	93.2	38.5	236.2
Los Angeles	119.7	39.2	330.3	125.6	39.0	352.4	121.5	40.0	334.9
Greater California	128.7	39.5	362.3	133.4	40.2	377.5	115.2	41.8	307.3
Connecticut	137.4	48.2	371.1	140.0	49.0	378.2	112.9	41.8	299.3
Detroit	130.9	44.1	358.1	135.4	45.3	371.1	121.6	41.8	330.5
Hawaii	124.2	45.1	331.4	144.8	47.2	400.2	74.7	-	238.3
Iowa	125.9	40.9	348.3	125.7	40.9	347.9	109.3	35.1	303.6
Kentucky	122.1	41.6	333.0	121.0	40.7	331.3	129.8	46.7	347.5
Louisiana	122.0	40.9	334.3	121.6	37.3	342.3	123.7	49.2	319.0
New Jersey	131.7	46.8	354.0	136.5	48.5	367.2	112.2	41.1	298.5
New Mexico	112.2	36.8	309.7	118.3	39.0	326.0	68.5	23.9	185.4
Seattle-Puget Sound	145.8	43.8	412.7	151.9	44.3	433.8	113.7	44.1	295.8
Utah	115.7	34.7	328.0	117.5	35.0	333.3	82.9	-	-
9 SEER Areas[b]	131.0	43.0	361.5	136.5	43.5	379.8	117.8	42.0	316.3
11 SEER Areas[b]	128.0	42.0	353.5	134.1	42.4	374.2	118.5	41.5	320.3
13 SEER Areas[b]	128.0	42.0	353.3	134.0	42.4	374.0	118.3	41.5	319.4
17 SEER Areas[b]	127.8	41.9	353.0	132.5	42.2	369.1	118.3	42.9	315.8

[a] Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130)
[b] The SEER 9 areas are San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah and Atlanta.
The SEER 11 areas comprise the SEER 9 areas plus San Jose-Monterey and Los Angeles.
The SEER 13 areas comprise the SEER 11 areas plus the Alaska Native Registry and Rural Georgia.
The SEER 17 areas comprise the SEER 13 areas plus California excluding SF/SJM/LA, Kentucky, Louisiana and New Jersey

- Statistic not shown. Rate based on less than 16 cases for the time interval.

Table IV-18
FEMALE BREAST CANCER (Invasive)

AGE-ADJUSTED SEER DEATH RATES[a]
By Registry, Race/Ethnicity and Age

	All Races			Whites			Blacks		
	All Ages	Ages <50	Ages 50+	All Ages	Ages <50	Ages 50+	All Ages	Ages <50	Ages 50+
SEER DEATH RATES[a], 2000-2004									
REGISTRY									
Atlanta & Rural Georgia	26.4	5.8	80.2	24.3	4.1	77.3	32.3	8.7	94.0
Atlanta	26.6	5.8	81.3	24.5	4.1	78.1	32.9	8.7	96.5
Rural Georgia	22.7	-	64.7	19.3	-	62.4	26.1	-	66.2
California	24.2	5.4	73.2	25.0	5.2	76.8	33.7	10.4	94.8
Greater Bay Area	23.6	5.1	72.0	25.5	4.7	80.0	33.2	10.9	91.6
San Francisco-Oakland	24.8	5.4	75.4	26.8	4.8	84.4	33.8	11.1	93.2
San Jose-Monterey	21.3	4.6	65.2	23.2	4.5	72.1	28.5	-	77.8
Los Angeles	23.5	5.5	70.6	23.8	5.0	73.0	34.1	10.7	95.2
Greater California	24.7	5.5	74.9	25.3	5.5	77.3	33.8	9.8	96.6
Connecticut	25.2	5.1	77.9	25.2	4.9	78.2	26.9	6.9	79.2
Detroit	28.1	6.2	85.3	26.0	5.1	80.6	35.8	9.6	104.3
Hawaii	17.3	4.5	50.8	22.9	4.9	70.1	-	-	-
Iowa	23.6	4.6	73.2	23.4	4.6	72.8	37.2	-	111.0
Kentucky	26.2	5.6	79.9	25.5	5.3	78.5	36.6	9.6	107.5
Louisiana	29.8	7.5	88.3	25.7	5.3	79.4	40.3	12.3	113.7
New Jersey	28.5	5.3	89.1	28.3	4.9	89.6	34.6	8.9	102.0
New Mexico	22.6	5.7	66.7	23.4	6.0	68.9	24.8	-	86.3
Seattle-Puget Sound	23.7	4.4	74.4	24.4	4.2	77.1	29.9	9.5	83.2
Utah	23.0	4.5	71.5	23.2	4.5	72.2	-	-	-
9 SEER Areas[b]	24.6	5.2	75.4	24.7	4.7	77.1	33.1	9.0	96.3
11 SEER Areas[b]	24.2	5.2	73.8	24.5	4.8	76.0	33.2	9.4	95.7
13 SEER Areas[b]	24.2	5.2	73.7	24.4	4.8	75.9	33.1	9.4	95.2
17 SEER Areas[b]	25.3	5.5	77.2	25.3	5.0	78.5	34.9	9.8	100.4
Total U.S.	25.5	5.6	77.7	25.0	5.1	77.0	33.8	9.8	96.9

[a] NCHS public use data file for the total US. Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130).

[b] The SEER 9 areas are San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah and Atlanta.
The SEER 11 areas comprise the SEER 9 areas plus San Jose-Monterey and Los Angeles.
The SEER 13 areas comprise the SEER 11 areas plus the Alaska Native Registry and Rural Georgia.
The SEER 17 areas comprise the SEER 13 areas plus California excluding SF/SJM/LA, Kentucky, Louisiana and New Jersey

- Statistic not shown. Rate based on less than 16 cases for the time interval.

Table IV-19
FEMALE BREAST CANCER (*In Situ*)

AGE-ADJUSTED SEER INCIDENCE RATES[a]
By Registry, Race/Ethnicity and Age

	All Races			Whites			Blacks		
	All Ages	Ages <50	Ages 50+	All Ages	Ages <50	Ages 50+	All Ages	Ages <50	Ages 50+
SEER INCIDENCE RATES[a], 2000-2004									
REGISTRY									
Atlanta & Rural Georgia	32.6	11.1	89.0	36.3	12.9	97.7	27.0	8.6	75.1
Atlanta	33.0	11.2	90.1	36.6	12.8	99.0	27.4	8.9	76.0
Rural Georgia	26.7	9.7	71.2	32.1	16.0	74.1	19.5	-	63.0
California	26.9	9.2	73.5	27.6	9.2	75.6	23.3	7.0	66.1
Greater Bay Area	30.1	10.9	80.2	31.0	10.7	84.2	22.7	6.7	64.4
San Francisco-Oakland	31.0	11.4	82.4	32.2	11.5	86.4	23.1	6.8	65.9
San Jose-Monterey	28.2	10.1	75.7	28.8	9.3	80.1	18.7	-	50.6
Los Angeles	24.8	8.7	66.8	25.6	8.9	69.4	24.0	7.5	67.1
Greater California	26.9	8.8	74.2	27.4	9.0	75.6	23.1	6.6	66.3
Connecticut	42.5	17.3	108.7	43.5	18.0	110.1	31.6	9.8	88.4
Detroit	38.1	14.3	100.4	39.7	15.8	102.3	34.4	10.2	97.7
Hawaii	35.2	12.6	94.6	32.8	10.5	91.1	-	-	-
Iowa	25.8	9.3	69.1	25.7	9.2	69.0	24.2	-	69.7
Kentucky	23.4	8.4	62.7	23.2	8.5	61.7	23.6	5.8	70.3
Louisiana	22.0	7.6	59.5	23.0	8.1	61.9	19.9	6.6	54.6
New Jersey	35.2	15.1	87.9	37.2	16.3	91.9	25.1	8.8	67.7
New Mexico	20.8	6.7	57.7	22.4	7.5	61.3	-	-	-
Seattle-Puget Sound	35.2	11.4	97.5	35.9	11.8	99.2	32.4	6.5	100.5
Utah	23.7	7.5	66.3	24.0	7.4	67.4	-	-	-
9 SEER Areas[b]	32.9	11.9	88.0	33.7	12.3	89.6	29.7	8.9	84.3
11 SEER Areas[b]	30.8	11.0	82.5	31.7	11.4	84.8	28.0	8.5	79.1
13 SEER Areas[b]	30.8	11.0	82.5	31.7	11.4	84.8	27.9	8.5	78.9
17 SEER Areas[b]	29.4	10.6	78.6	30.2	11.0	80.5	25.4	7.9	71.2

[a] Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130)
[b] The SEER 9 areas are San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah and Atlanta.
The SEER 11 areas comprise the SEER 9 areas plus San Jose-Monterey and Los Angeles.
The SEER 13 areas comprise the SEER 11 areas plus the Alaska Native Registry and Rural Georgia.
The SEER 17 areas comprise the SEER 13 areas plus California excluding SF/SJM/LA, Kentucky, Louisiana and New Jersey

\- Statistic not shown. Rate based on less than 16 cases for the time interval.

Table IV-20
FEMALE BREAST CANCER (Invasive)

AVERAGE ANNUAL AGE-ADJUSTED CANCER DEATH[a] RATES BY STATE, ALL RACES, 2000-2004

Females

State	Rate	SE	Rank	PD
TOTAL U.S.	25.5	0.06		
High Five States				
District of Columbia	32.1[b]	1.42	(01)	25.9[c]
Louisiana	29.8[b]	0.50	(02)	16.9[c]
New Jersey	28.5[b]	0.33	(03)	11.8[c]
Ohio	28.0[b]	0.29	(04)	9.8
Mississippi	27.8[b]	0.60	(05)	9.0
Low Five States				
Utah	23.0[b]	0.71	(47)	-9.8
Colorado	23.0[b]	0.47	(48)	-9.8
New Mexico	22.6[b]	0.68	(49)	-11.4[c]
Alaska	22.4	1.51	(50)	-12.2[c]
Hawaii	17.3[b]	0.70	(51)	-32.2[c]

State	Rate	SE	Rank	PD
Alabama	26.0	0.45	(17)	2.0
Alaska	22.4	1.51	(50)	-12.2[c]
Arizona	23.4[b]	0.40	(45)	-8.2
Arkansas	24.4	0.55	(32)	-4.3
California	24.2[b]	0.17	(33)	-5.1
Colorado	23.0[b]	0.47	(48)	-9.8
Connecticut	25.2	0.49	(27)	-1.2
Delaware	26.6	1.07	(11)	4.3
District of Columbia	32.1[b]	1.42	(01)	25.9[c]
Florida	23.5[b]	0.21	(44)	-7.8
Georgia	25.5	0.35	(23)	0.0
Hawaii	17.3[b]	0.70	(51)	-32.2[c]
Idaho	23.7	0.84	(40)	-7.1
Illinois	27.0[b]	0.28	(09)	5.9
Indiana	26.2	0.39	(14)	2.7
Iowa	23.6[b]	0.51	(43)	-7.5
Kansas	25.2	0.57	(28)	-1.2
Kentucky	26.2	0.47	(15)	2.7
Louisiana	29.8[b]	0.50	(02)	16.9[c]
Maine	23.7	0.76	(41)	-7.1
Maryland	27.6[b]	0.43	(06)	8.2
Massachusetts	25.6	0.36	(22)	0.4
Michigan	25.8	0.30	(20)	1.2
Minnesota	23.9[b]	0.42	(37)	-6.3
Mississippi	27.8[b]	0.60	(05)	9.0
Missouri	26.6	0.40	(10)	4.3

State	Rate	SE	Rank	PD
Montana	24.0	0.94	(35)	-5.9
Nebraska	23.6	0.69	(42)	-7.5
Nevada	26.2	0.71	(16)	2.7
New Hampshire	24.8	0.83	(29)	-2.7
New Jersey	28.5[b]	0.33	(03)	11.8[c]
New Mexico	22.6[b]	0.68	(49)	-11.4[c]
New York	26.2	0.22	(13)	2.7
North Carolina	25.4	0.33	(24)	-0.4
North Dakota	24.0	1.12	(36)	-5.9
Ohio	28.0[b]	0.29	(04)	9.8
Oklahoma	25.6	0.51	(21)	0.4
Oregon	25.2	0.50	(26)	-1.2
Pennsylvania	27.5[b]	0.26	(07)	7.8
Rhode Island	24.0	0.86	(34)	-5.9
South Carolina	25.9	0.47	(18)	1.6
South Dakota	23.7	1.04	(39)	-7.1
Tennessee	26.3	0.40	(12)	3.1
Texas	24.5[b]	0.22	(30)	-3.9
Utah	23.0[b]	0.71	(47)	-9.8
Vermont	25.8	1.18	(19)	1.2
Virginia	27.2[b]	0.37	(08)	6.7
Washington	23.8[b]	0.39	(38)	-6.7
West Virginia	25.4	0.66	(25)	-0.4
Wisconsin	24.5	0.40	(31)	-3.9
Wyoming	23.2	1.32	(46)	-9.0

[a] NCHS public use data file. Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130).
[b] Difference between state rate and total U.S. rate is statistically significant (p<=.0002).
[c] Absolute percent difference between state rate and total U.S. rate is 10% or more.
SE Standard error of the rate.
PD Percent difference between state rate and total U.S. rate.

Table IV-21
BREAST CANCER (Invasive)

Estimated United States Cancer Prevalence Counts[a] on January 1, 2004
By Race/Ethnicity, Sex and Years Since Diagnosis

Years Since Diagnosis	0 to <5	5 to <10	10 to <15	15 to <20	20 to <25	0 to <14[e]	0 to <29[e]	>=29[g]	Complete[h]
Race/Sex									
All Races[b]	819,033	604,268	407,714	261,657	138,936	1,763,214	2,311,009	109,204	2,420,213
Males	5,334	2,860	1,694	1,016	758	9,673	11,962	308	12,270
Females	813,699	601,408	406,020	260,641	138,178	1,753,541	2,299,047	108,896	2,407,943
White[b]	716,788	538,074	367,895	239,127	126,620	1,561,045	2,061,456	97,253	2,158,709
Males	4,528	2,533	1,463	904	724	8,338	10,440	181[i]	10,621
Females	712,260	535,541	366,432	238,223	125,896	1,552,707	2,051,016	97,072	2,148,088
Black[b]	70,732	45,895	28,262	16,372	9,016	140,495	174,874	+	+
Males	664	217	197	96	30	1,053	1,217	+	+
Females	70,068	45,678	28,065	16,276	8,986	139,442	173,657	7,527	181,184
Asian/Pacific Islander[c]	22,676	14,429	+	+	+	44,218	+	+	+
Males	77	55	+	+	+	163	+	+	+
Females	22,599	14,374	+	+	+	44,055	+	+	+
Hispanic[d]	40,609	25,430	+	+	+	79,851	+	+	+
Males	157	76	+	+	+	266	+	+	+
Females	40,452	25,354	+	+	+	79,585	+	+	+

Estimated prevalence percent[a] on January 1, 2004, of the SEER 11 population diagnosed in the previous 10 years
By Age at Prevalence, Race/Ethnicity and Sex

Age at Prevalence	Age Specific (Crude)										Age-Adjusted[f]
	All Ages	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80+	All Ages
Race/Sex											
All Races[c]	0.4389%	-	0.0002%	0.0051%	0.0761%	0.3795%	0.9238%	1.4648%	1.8751%	1.9770%	0.4564%
Males	0.0050%	-	-	-	0.0005%	0.0024%	0.0082%	0.0205%	0.0314%	0.0398%	0.0061%
Females	0.8634%	-	0.0004%	0.0103%	0.1542%	0.7536%	1.7918%	2.7575%	3.2667%	3.0382%	0.8342%
White[c]	0.4810%	-	0.0002%	0.0050%	0.0750%	0.3852%	0.9594%	1.5602%	2.0095%	2.1014%	0.4797%
Males	0.0054%	-	-	-	0.0005%	0.0023%	0.0082%	0.0206%	0.0334%	0.0413%	0.0062%
Females	0.9550%	-	0.0003%	0.0103%	0.1552%	0.7777%	1.8884%	2.9745%	3.5326%	3.2150%	0.8856%
Black[c]	0.3044%	-	-	0.0064%	0.0894%	0.3602%	0.8268%	1.2201%	1.5701%	1.6334%	0.3988%
Males	0.0052%	-	-	-	-	0.0040%	0.0131%	0.0369%	0.0298%	0.0426%	0.0081%
Females	0.5752%	-	-	0.0123%	0.1677%	0.6722%	1.5005%	2.1463%	2.5797%	2.4005%	0.6876%
Asian/Pacific Islander[c]	0.3141%	-	-	0.0046%	0.0703%	0.3597%	0.7675%	1.0208%	1.1634%	1.0529%	0.3303%
Males	0.0025%	-	-	-	-	-	0.0042%	0.0080%	0.0169%	0.0242%	0.0031%
Females	0.6056%	-	-	0.0091%	0.1366%	0.6852%	1.4356%	1.8696%	1.9860%	1.7371%	0.5982%
Hispanic[d]	0.1640%	-	-	0.0043%	0.0490%	0.2696%	0.6173%	0.9534%	1.1581%	1.1752%	0.2969%
Males	0.0011%	-	-	-	-	0.0011%	0.0040%	0.0096%	0.0089%	0.0144%	0.0024%
Females	0.3357%	-	-	0.0093%	0.1051%	0.5485%	1.1887%	1.7384%	1.9791%	1.8386%	0.5409%

a US 2004 cancer prevalence counts are based on 2004 cancer prevalence proportions from the SEER registries and 1/1/2004 US population estimates based on the average of 2003 and 2004 population estimates from the US Bureau of the Census. Prevalence was calculated using the First Malignant Primary Only for a person.

b c d Statistics based on (b) SEER 9 Areas (c) SEER 11 Areas and Rural Georgia (d) NHIA for Hispanic for SEER 11 Areas and Rural Georgia.

e Maximum limited-duration prevalence: 29 years for 1975-2004 SEER 9 data; 14 years for 1990-2004 SEER 11 data (used to calculate prevalence for Hispanics and Asian Pacific Islanders).

f Percentages are age-adjusted to the 2000 US Standard Population (19 age groups - Census P25-1130) by 5-year age groups.

g h i (g) Cases diagnosed more than 29 years ago were estimated using the completeness index method (Capocaccia et. al. 1997, Merrill et. al. 2000). (h)Complete prevalence is obtained by summing 0 to <29 and >=29. (i)Age-specific completeness index was approximated using empirical data from historical Connecticut tumor registry.

- Statistic not shown. Statistic based on fewer than 5 cases estimated alive in SEER for the time interval.

+ Not available.

Table IV-22

FEMALE BREAST CANCER (Invasive)

Percent Distribution and Counts by Histology among Histologically Confirmed Cases, 2001-2004
Females by Race

Histology	All Races		White		Black	
	Count	Percent	Count	Percent	Count	Percent
Adenocarcinoma	190,485	96.9%	159,874	97.1%	16,582	95.4%
Adenocarcinoma, NOS (8140)	2,125	1.1%	1,708	1.0%	278	1.6%
Infiltrating duct carcinoma (8500)	132,336	67.3%	109,644	66.6%	12,206	70.2%
Infiltrating lobular carcinoma, NOS (8520)	15,734	8.0%	14,099	8.6%	970	5.6%
Inflammatory adenocarcinoma (8230)	131	0.1%	117	0.1%	-	-
Infiltrating duct and lobular carcinoma (8522-8524)	24,891	12.7%	21,683	13.2%	1,656	9.5%
Mucinous and mucin-producing adenocarcinoma (8480,8481)	5,094	2.6%	4,203	2.6%	411	2.4%
Tubular adenocarcinoma (8211)	3,154	1.6%	2,867	1.7%	119	0.7%
Papillary adenocarcinoma (8260, 8503, 8504)	732	0.4%	536	0.3%	110	0.6%
Paget disease (8540-8543)	1,084	0.6%	899	0.5%	101	0.6%
Medullary adenocarcinoma (8510-8513)	1,382	0.7%	973	0.6%	310	1.8%
Other adenocarcinomas[a]	3,822	1.9%	3,145	1.9%	409	2.4%
Sarcoma	655	0.3%	500	0.3%	69	0.4%
Cystosarcoma phyllodes (9020)	470	0.2%	345	0.2%	53	0.3%
Hemangiosarcomas (9120-9126, 9170)	115	0.1%	99	0.1%	-	-
Other sarcomas (8890, 8935, 8980)	70	0.0%	56	0.0%	-	-
Other malignant histologies	5,395	2.7%	4,273	2.6%	734	4.2%
Total	196,535	100.0%	164,647	100.0%	17,385	100.0%

Source: SEER 17 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana and New Jersey). Percents may not sum to 100 due to rounding.
- Statistic not shown due to fewer than 16 cases during the time period.
[a] Includes histologies 8141-8210, 8212-8229, 8231-8259, 8261-8389, 8401, 8408, 8410, 8411, 8413, 8441, 8450, 8460, 8470 8482, 8490, 8525, 8530, 8571-8574, 8576, 8650, 9070, 9110.

Table IV-23

FEMALE BREAST CANCER (*In Situ*)

Percent Distribution and Counts by Histology among Histologically Confirmed Cases, 2001-2004
Females by Race

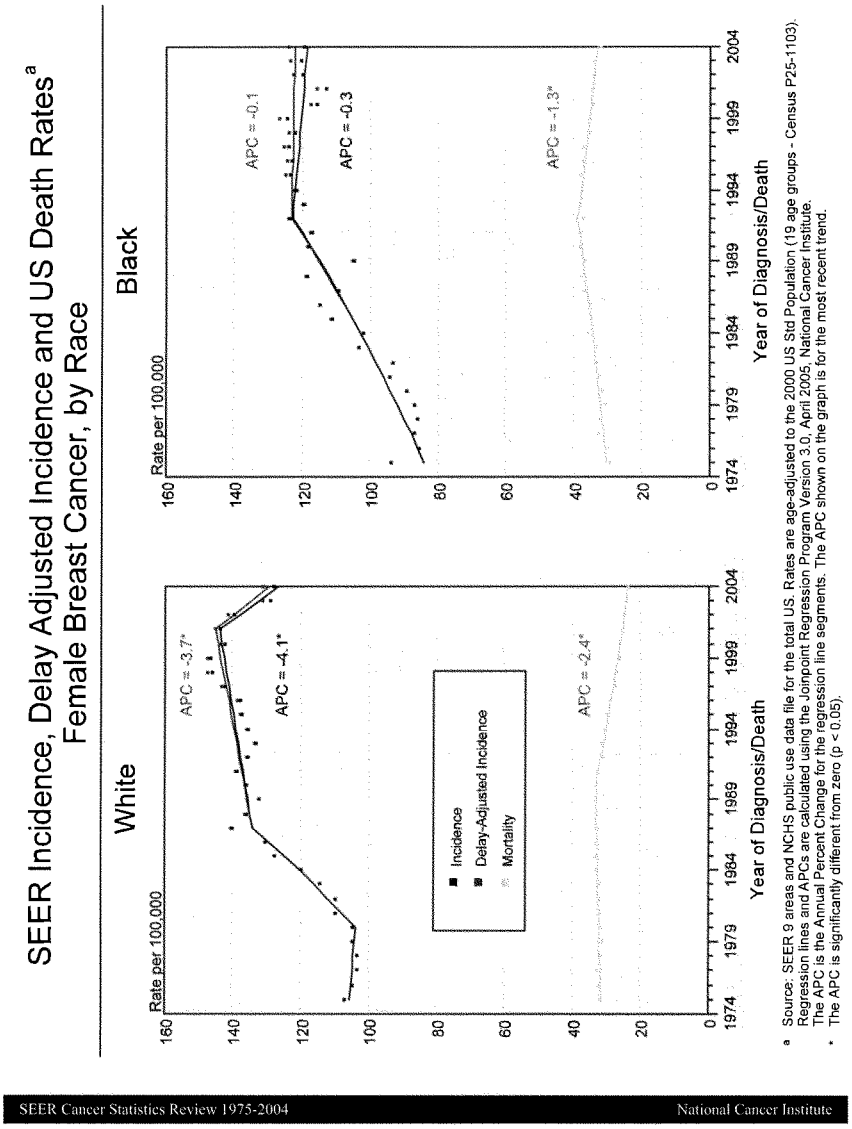
Histology	All Races		White		Black	
	Count	Percent	Count	Percent	Count	Percent
Adenocarcinoma	36,820	79.8%	30,533	80.4%	3,000	77.9%
Adenocarcinoma *in situ*, NOS (8140/2)	16	0.0%	16	0.0%	-	-
Cribiform carcinoma *in situ* (8201/2)	3,674	8.0%	2,983	7.9%	269	7.0%
Ductal carcinoma *in situ* (8230/2, 8500/2)	18,368	39.8%	15,049	39.6%	1,592	41.4%
Lobular carcinoma *in situ*, NOS (8520/2)	5,244	11.4%	4,616	12.2%	312	8.1%
Comedocarcinoma *in situ* (8501/2)	4,518	9.8%	3,789	10.0%	341	8.9%
Intraductal and lobular carcinoma *in situ* (8522/2)	1,867	4.0%	1,591	4.2%	144	3.7%
Intraductal micropapillary (8507/2)	1,613	3.5%	1,311	3.5%	167	4.3%
Other adenocarcinomas[a]	1,520	3.3%	1,178	3.1%	175	4.5%
Other *in situ* histologies	9,305	20.2%	7,458	19.6%	849	22.1%
Total	46,125	100.0%	37,991	100.0%	3,849	100.0%

Source: SEER 17 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana and New Jersey). Percents may not sum to 100 due to rounding.

\- Statistic not shown due to fewer than 16 cases during the time period.

[a] Includes histologies 8141-8200, 8202-8229, 8231-8389, 8401, 8408, 8410, 8411, 8413, 8441, 8450, 8460, 8470 8480-8482, 8490, 8503, 8504, 8510, 8525, 8530, 8560, 8571-8574, 8576, 9070, 9110.

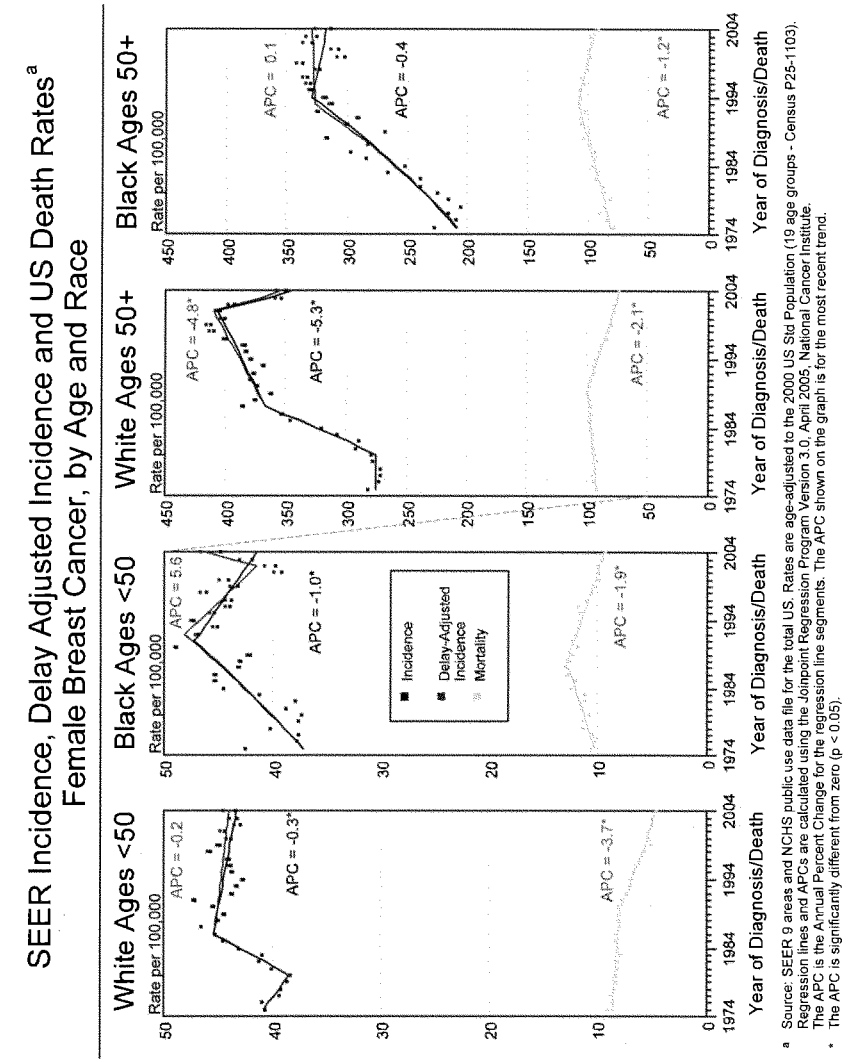
Figure IV-1



[a] Source: SEER 9 areas and NCHS public use data file for the total US. Rates are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1103). Regression lines and APCs are calculated using the Joinpoint Regression Program Version 3.0, April 2005, National Cancer Institute. The APC is the Annual Percent Change for the regression line segments. The APC shown on the graph is for the most recent trend.

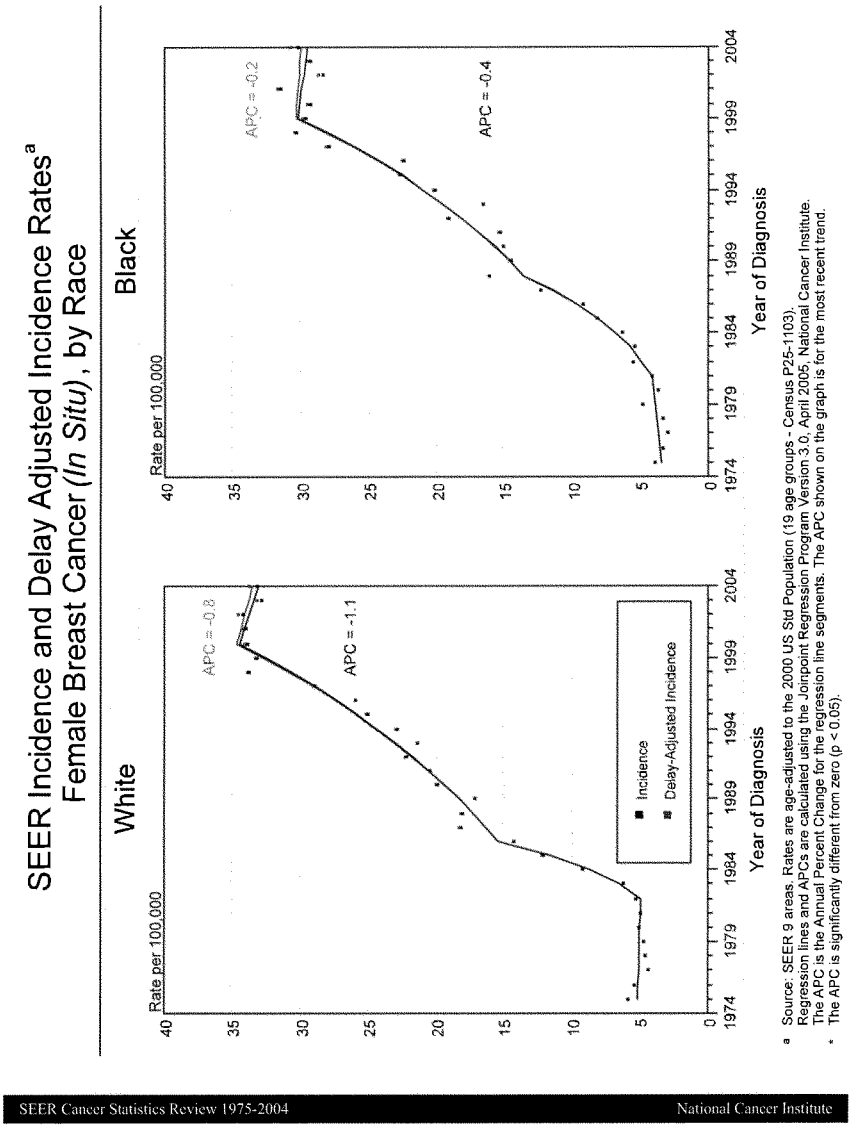
* The APC is significantly different from zero ($p < 0.05$).

Figure IV-2



[a] Source: SEER 9 areas and NCHS public use data file for the total US. Rates are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1103). Regression lines and APCs are calculated using the Joinpoint Regression Program Version 3.0, April 2005, National Cancer Institute.
The APC is the Annual Percent Change for the regression line segments. The APC shown on the graph is for the most recent trend.
* The APC is significantly different from zero ($p < 0.05$).

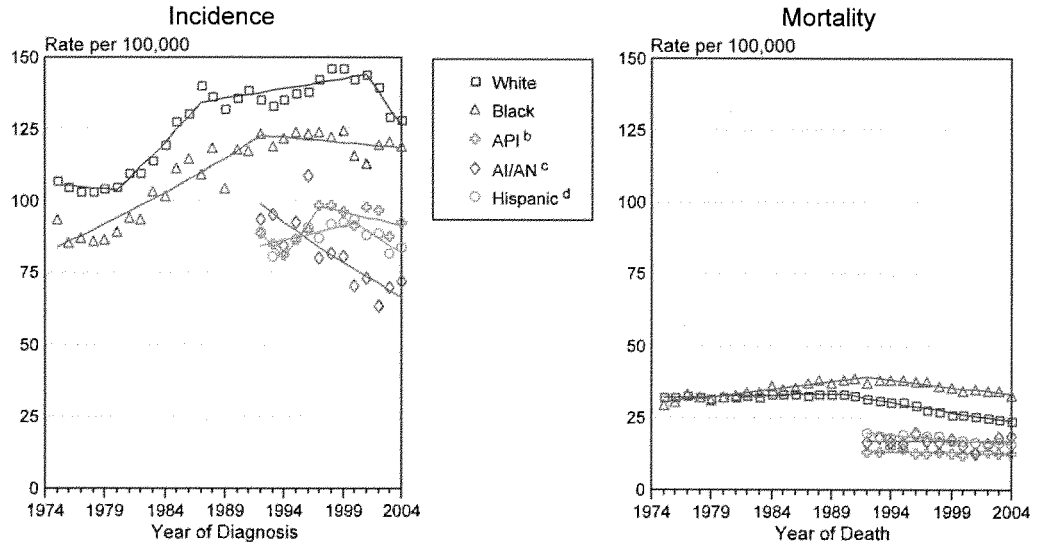
Figure IV-3



[a] Source: SEER 9 areas. Rates are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1103). Regression lines and APCs are calculated using the Joinpoint Regression Program Version 3.0, April 2005, National Cancer Institute. The APC is the Annual Percent Change for the regression line segments. The APC shown on the graph is for the most recent trend.

* The APC is significantly different from zero ($p < 0.05$).

SEER Incidence and US Death Rates[a]
Female Breast Cancer
Joinpoint Analyses for Whites and Blacks from 1975-2004
and for Asian/Pacific Islanders, American Indians/Alaska Natives and Hispanics from 1992-2004



Source: Incidence data for whites and blacks are from the SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta). Incidence data for Asian/Pacific Islanders, American Indians/Alaska Natives and Hispanics are from the SEER 13 Areas (SEER 9 Areas, San Jose-Monterey, Los Angeles, Alaska Native Registry and Rural Georgia). Mortality data are from NCHS public use data file for the total US.

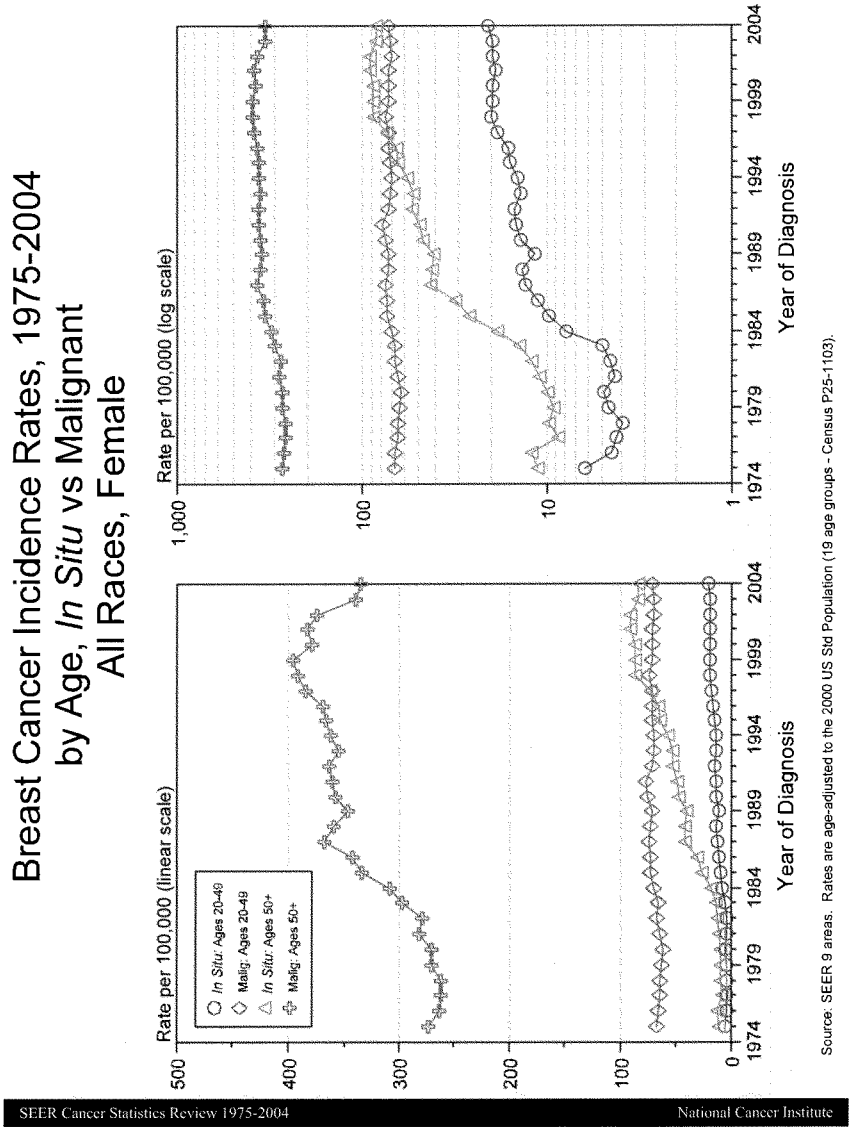
[a] Rates are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1103). Regression lines are calculated using the Joinpoint Regression Program Version 3.0, April 2005, National Cancer Institute.

[b] API = Asian/Pacific Islander.

[c] AI/AN = American Indian/Alaska Native. Rates for American Indian/Alaska Native are based on the CHSDA(Contract Health Service Delivery Area) counties.

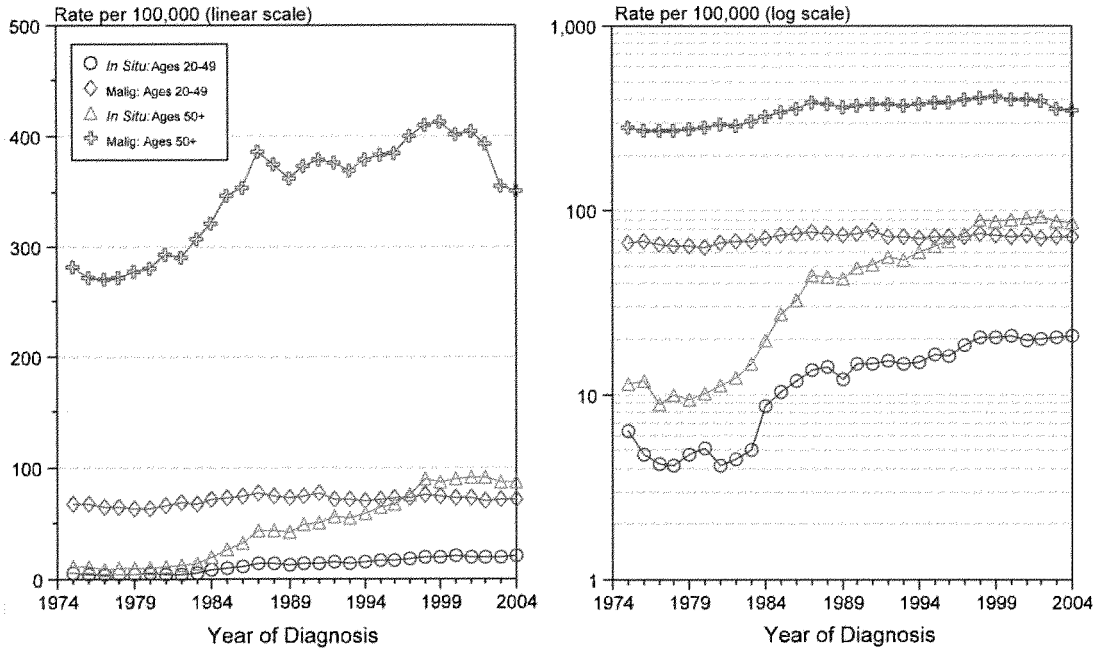
[d] Hispanic is not mutually exclusive from whites, blacks, Asian/Pacific Islanders, and American Indians/Alaska Natives. Incidence data for Hispanics are based on NHIA and exclude cases from the Alaska Native Registry. Mortality data for Hispanics exclude cases from Connecticut, Maine, Maryland, Minnesota, New Hampshire, New York, North Dakota, Oklahoma, and Vermont.

Figure IV-5



Source: SEER 9 areas. Rates are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1103).

Breast Cancer Incidence Rates, 1975-2004 by Age, *In Situ* vs Malignant White Female



Source: SEER 9 areas. Rates are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1103).

Figure IV-6

Figure IV-7

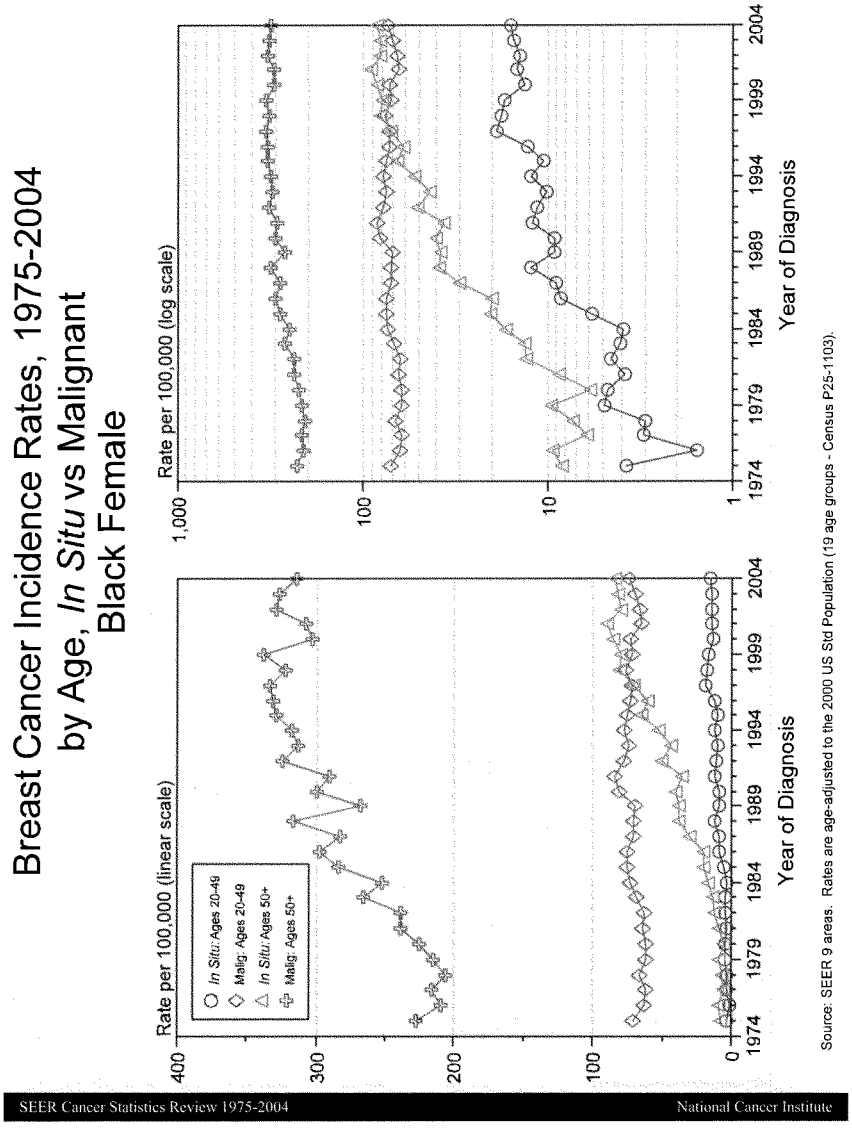
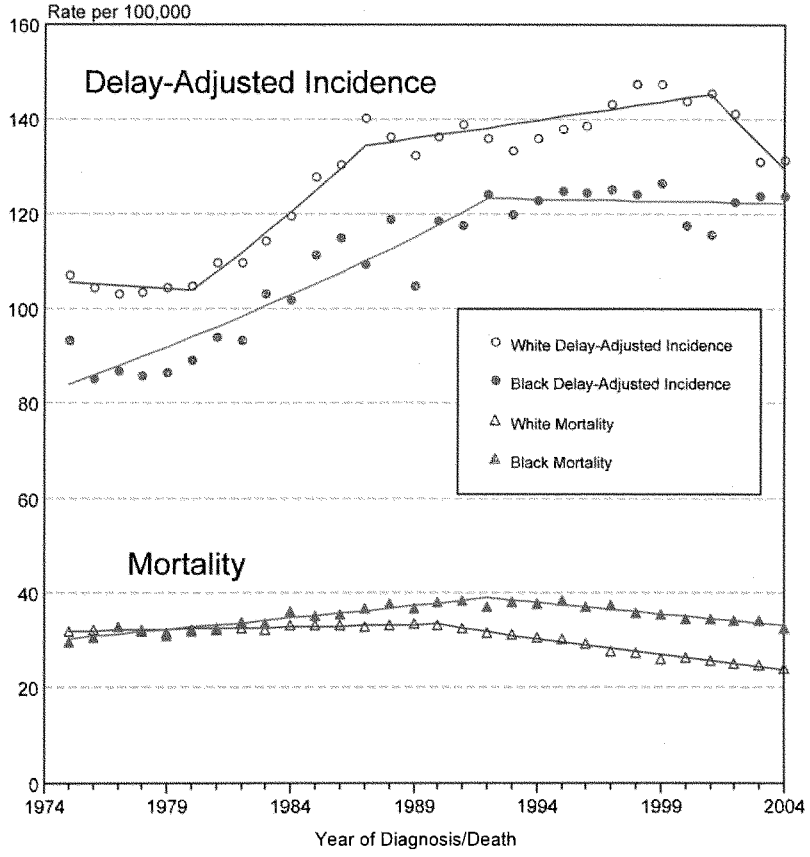

Breast Cancer Incidence Rates, 1975-2004
by Age, In Situ vs Malignant
Black Female
Rate per 100,000 (linear scale)
Rate per 100,000 (log scale)
In Situ: Ages 20-49
Malig: Ages 20-49
In Situ: Ages 50+
Malig: Ages 50+
Year of Diagnosis
Year of Diagnosis
Source: SEER 9 areas. Rates are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1103).
SEER Cancer Statistics Review 1975-2004
National Cancer Institute

Figure IV-8

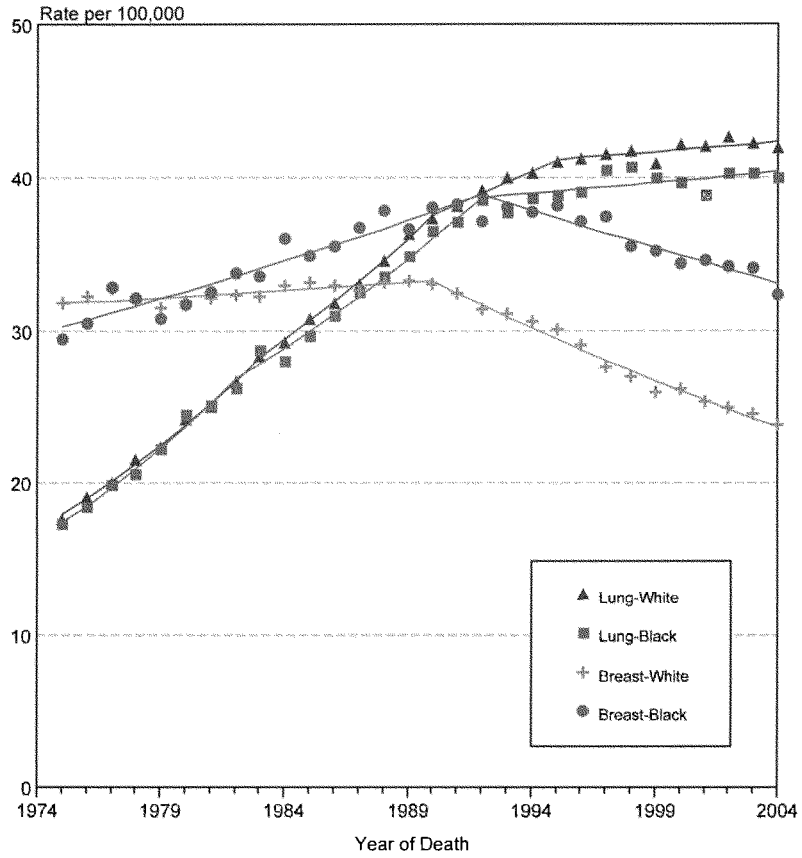
Breast Cancer Delay-Adjusted Incidence & Mortality White Females vs Black Females 1975-2004



Source: SEER 9 areas and NCHS public use data file for the total US.
Rates are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1103).
Regression lines are calculated using the Joinpoint Regression Program Version 3.0, April 2005, National Cancer Institute.

Figure IV-9

Breast vs Lung Cancer Mortality
White Females vs Black Females
1975-2004



Source: NCHS public use data file for the total US.
Rates are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1103).
Regression lines are calculated using the Joinpoint Regression Program Version 3.0, April 2005, National Cancer Institute.

Testis Cancer

Mitchell H. Sokoloff,* Geoffrey F. Joyce, Matthew Wise and the Urologic Diseases in America Project

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Purpose: We quantified the burden of testis cancer in the United States by identifying trends in its incidence, its treatment and the use of health care resources to estimate the economic impact of the disease.
Materials and Methods: The analytical methods used to generate these results were described previously.
Results: The overall incidence of testis cancer in the United States increased 46% between 1975 and 2001. During the same period the ratio of seminoma to nonseminoma increased and there were fewer men presenting with stage II and III tumors. Survival rates increased successively, attaining the current level of 95.9%. Treatment patterns changed and active surveillance increased as a primary treatment modality. Overall hospitalization rates for men with testis cancer decreased from 1.8/100,000 in 1994 and 1.4/100,000 in 2000. Care for white men shifted to the outpatient setting, which did not occur for black men. The estimated annual expenditure for testis cancer for privately insured individuals between ages 18 and 54 years was $6,236. National estimates of annual medical expenditures placed the total cost of treatment at $21.8 million in 2000, representing an increase of 10% over the total in 1994. Of men with testis cancer 16% missed work for treatment of the disease with an average of 8.4 total hours of work missed.
Conclusions: The cost of testis cancer is estimated at almost $21.8 million annually. It appears to be increasing with time despite a shift to active surveillance treatments and less hospitalization.

Key Words: testis, testicular neoplasms, health care costs, hospitalization, prevalence

The incidence of testis cancer is increasing. In 2005 approximately 8,000 new cases were diagnosed in the United States.[1] Because of advances in therapy, overall survival rates are high. Modifications in surgical and radiation techniques as well as improved methods of systemic chemotherapy have substantially decreased the morbidity of therapy. Nonetheless, the sequelae of multimodality therapy are not insignificant and they can have broad and far-reaching consequences with regard to general health, reproduction and economic productivity. We explored the burden of testis cancer in the United States by evaluating trends in incidence, mortality and treatment, quantifying the use of health care resources and estimating the economic impact of the disease.

MATERIALS AND METHODS

The analytical methods used to generate these results were described previously.[2,3]

RESULTS

Prevalence and Incidence

Testis cancer represents less than 1% of all male cancers.[4] According to the SEER database the age adjusted incidence rate of testis cancer from 1997 to 2001 was estimated to be 5.5/100,000 population. The overall incidence of testis cancer in the United States has been steadily increasing.[4] SEER data showed that the overall incidence of testicular germ cell tumors increased 46% between 1975 and 2001 from 3.7/100,000 to 5.4/100,000 population, which corresponds to an annual change of 1.5% across all populations under study (table 1).

Age. Testis cancer is being diagnosed at an earlier age. In men younger than 50 years in the SEER database the incidence of testis cancer increased from 4.2/100,000 to 6.7/100,000 between 1975 and 2001. During the same period the incidence in men older than 50 years decreased from 2.4/100,000 to 2.0/100,000. McKiernan et al reviewed similar SEER data on 1973 to 1995 and found that birth cohort was strongly associated with the relative risk of testis cancer and the peak age at diagnosis decreased for each successive birth cohort (fig. 1).[4]

Ethnicity. SEER data indicated that the lifetime risk of being diagnosed with testis cancer was 4 times greater for white men than for black men (table 2). The age adjusted incidence in 1997 to 2001 for white men was 6.2/100,000 population, while that for black men was 1.5/100,000. The age adjusted incidence in the Hispanic, Asian/Pacific Islander and Native American/Alaskan populations was between these rates. Between 1975 and 2001 the incidence of testis cancer in white men increased 54% from 4.1/100,000 to 6.3/100,000. In black men the overall incidence of testis cancer remained stable between 1973 and 1998 at about 0.9/100,000 to 1.04/100,000.[5]

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TABLE 1. *Age adjusted testicular cancer incidence rates by age*

Diagnosis Yr	All	Younger Than 50	50 or Older
1975	3.7	4.2	2.4
1976	3.4	4.2	1.5
1977	4.3	5.1	2.2
1978	3.6	4.2	1.8
1979	3.9	4.5	2.2
1980	4.4	5.3	1.9
1981	4.2	5.1	1.8
1982	4.4	5.2	2.3
1983	4.6	5.5	2.2
1984	4.4	5.3	1.9
1985	4.5	5.5	1.8
1986	4.8	5.8	2.2
1987	5.0	6.3	1.8
1988	4.6	5.8	1.5
1989	5.5	6.7	2.2
1990	5.1	6.8	2.1
1991	5.1	6.2	2.1
1992	5.2	6.4	1.9
1993	5.1	6.4	1.6
1994	5.5	6.7	2.1
1995	4.6	5.6	1.8
1996	5.2	6.6	1.7
1997	5.4	6.5	2.4
1998	5.6	7.1	1.6
1999	5.4	6.8	1.8
2000	5.7	7.1	2.0
2001	5.4	6.7	2.0
1997–2001	5.5	6.9	2.0

SEER 9 areas, rates per 100,000 and age adjusted to the 2000 standard population by 5-year age groups (source: SEER Program [www.seer.cancer.gov] SEER*Stat Database: Incidence–SEER 9 Regs Public Use, November 2004 Sub [1973–2002], National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2005, based on the November 2004 submission).

TABLE 2. *Age adjusted incidence rates for testicular cancer in 1997 to 2001 by race/ethnicity*

	1997–2001 Rate/100,000 Population	1992–2001 Annual % Change Trend
All	5.2	1.2*
White:	5.2	1.3*
Hispanic*	3.7	1.0
NonHispanic	7.0	1.8*
Black	1.5	6.4*
Asian/Pacific Islander	2.1	2.3
American Indian/Alaska native	2.3	Not available
Hispanic	3.6	1.1

Incidence data from the 12 SEER areas San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles and Alaska Native Registry, Hispanic and non-Hispanic not mutually exclusive from white, black, Asian/Pacific Islander and American Indian/Alaska natives, and Hispanic and nonHispanic incidence data do not include Detroit, Hawaii and Alaska Native Registry (source: SEER Program [www.seer.cancer.gov] SEER*Stat Database: Incidence–SEER 9 Regs Public Use, November 2004 Sub [1973–2002], National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2005, based on the November 2004 submission).

* Significantly different from zero ($p < 0.05$).

Histology. SEER data on 1973 to 1998 demonstrated that seminoma and nonseminoma have distinguishable incidence patterns in white and black racial groups (fig. 2).[5] For white men the incidence of seminoma increased, while the incidence of NSGCT decreased. In addition, the ratio of seminoma to nonseminoma in white men changed from 60/50 in 1973 to 1978, to 60/40 in 1994 to 1998. In black men seminoma also showed a continued increasing incidence coupled with an overall decrease in NSGCT. Moreover, the seminoma-to-nonseminoma ratio in black men increased from 60/40 to 70/30. Biggs and Schwartz evaluated the relationships between histology and ethnicity in their examination of 16,086 cases from the SEER database (table 3).[6] Seminomas represented an average of 56% of the cases under study from a low of 51% in Hispanic-American men to a high of 70% in Japanese-American men. Of the NSGCT subtypes mixed germ cell (mean 22%, range 14% to 29%) was the most common, followed by embryonal (mean 16%, range 9% to 17%) and then teratoma (mean 3%, range 0% to 5%), and finally choriocarcinoma and yolk sac (mean 1% each, range 0% to 3% and 0% to 2%, respectively). This order of histological frequency (mixed, embryonal, teratoma, choriocarcinoma and

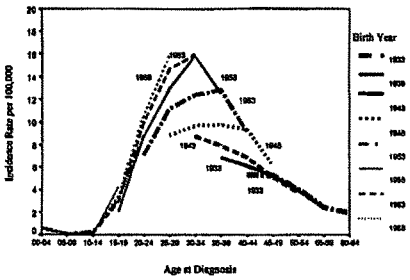

FIG. 1. Testicular cancer rates by birth cohort vs patient age at diagnosis.[4]

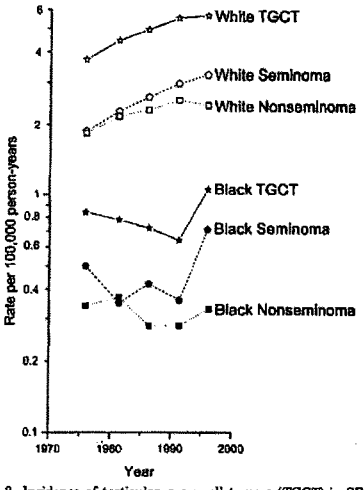

FIG. 2. Incidence of testicular germ cell tumors (*TGCT*) in SEER Program from 1973 to 1978 and 1994 to 1998 by patient race/ethnicity and tumor type.[5]

TABLE 3. *Characteristics of patients with testicular cancer by age and race/ethnicity*

	No. NonHispanic White (%)	No. Black (%)	No. Native American (%)	No. Chinese (%)	No. Japanese (%)	No. Filipino (%)	No. Hawaiian (%)	No. Hispanic White (%)	Total (%)
All	13,922	329	89	129	141	60	94	1,322	10,086
Diagnosis age:									
15–19	598 (4)	13 (4)	6 (7)	1 (1)	2 (1)	1 (2)	6 (6)	107 (8)	734 (5)
20–29	4,572 (33)	101 (31)	43 (48)	41 (32)	39 (28)	27 (45)	42 (45)	575 (44)	5,443 (34)
30–39	5,185 (37)	137 (42)	25 (29)	50 (39)	60 (43)	19 (32)	33 (35)	426 (32)	5,935 (37)
40–49	2,354 (17)	55 (17)	10 (11)	25 (19)	28 (20)	8 (13)	8 (9)	150 (11)	2,638 (16)
50–59	767 (6)	13 (4)	3 (3)	10 (8)	6 (4)	2 (3)	3 (3)	41 (3)	845 (5)
60 or Older	446 (3)	10 (3)	2 (2)	2 (2)	6 (4)	3 (5)	2 (2)	20 (2)	491 (3)
Diagnosis stage:									
Localized	9,084 (65)	202 (61)	51 (57)	98 (76)	100 (71)	43 (72)	47 (50)	841 (64)	10,466 (65)
Regional	2,896 (21)	65 (20)	13 (15)	16 (12)	25 (18)	10 (17)	22 (23)	248 (19)	3,295 (21)
Distant	1,640 (12)	53 (16)	24 (27)	12 (9)	15 (11)	6 (10)	25 (27)	213 (16)	1,988 (12)
Unstaged	302 (2)	9 (3)	1 (1)	3 (2)	1 (1)	1 (2)	0	20 (2)	337 (2)
Histology:									
Seminoma	7,779 (56)	197 (60)	47 (53)	84 (65)	99 (70)	39 (65)	49 (52)	678 (51)	6,972 (56)
NSGCT	5,995 (43)	119 (36)	40 (45)	39 (30)	42 (30)	20 (33)	44 (47)	635 (48)	6,934 (43)
Embryonical	2,318 (17)	33 (10)	12 (13)	15 (12)	12 (9)	6 (10)	16 (17)	182 (14)	2,594 (16)
Yolk sac	118 (1)	3 (1)	1 (1)	0	0	0	2 (2)	14 (1)	138 (1)
Teratoma	447 (3)	8 (2)	4 (4)	3 (2)	5 (4)	0	5 (5)	50 (4)	533 (3)
Chorioca	124 (1)	7 (2)	3 (3)	3 (2)	0	0	1 (1)	11 (1)	149 (1)
Mixed germ cell	2,988 (21)	68 (21)	20 (22)	18 (14)	25 (18)	14 (23)	20 (21)	378 (29)	3,531 (22)
Nongerm cell	146 (1)	13 (4)	2 (2)	6 (5)	0	1 (2)	1 (1)	9 (1)	180 (1)

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yolk sac) was found across all ethnic groups. Black, Native American, Hawaiian-American and Hispanic patients with testis cancer were more likely than white patients to have more aggressive NSGCT.

Stage. NCDB data from 1985 to 1991 indicated that the proportion of tumors presenting as stage I remained relatively stable at approximately 65%, whereas the percent of stage II and III tumors decreased from 12.9% to 6.1% and 8.9% to 6.7%, respectively (table 4). Stage IV tumors increased from 14% to 22% during the same period. The stage distribution of men in the SEER database from 1995 to 2000 showed 70% had localized disease, 18% had regional spread, 10% had distant spread and 1% had unstaged disease. White men were more likely to present with localized disease than were black men (71% vs 63%), who conversely were more likely to have metastatic disease (20% vs 18% and 16% vs 10% for regional and distant spread, respectively). Biggs and Schwartz evaluated the relationships between stage and ethnicity in the SEER database and found that an average of 65% of patients presented with localized disease, which is similar to findings in the NCDB data.[6] However, black, Native American, Hawaiian-American and Hispanic patients with testis cancer were more likely than white men to be diagnosed with late stage disease. Overall 21% of men presented with regional metastases and 12% presented with distant metastases.

Survival and Mortality

Survival. According to the SEER database from 1974 to the current 5-year survival rates increased successively, at-

TABLE 4. *Testicular tumor characteristics*[7]

	No. 1985–1986 (%)	No. 1990–1991 (%)	No. 1995–1996 (%)
Anatomical site:			
Undescended testis	39 (1.7)	138 (2.4)	160 (2.1)
Descended testis	56 (2.5)	278 (4.9)	2,187 (29.3)
Testis NOS	2,185 (95.8)	5,261 (92.7)	5,105 (68.5)
Totals	2,280 (100.0)	5,677 (100.0)	7,452 (100.0)
Histology:			
Seminoma NOS	1,219 (53.5)	3,029 (53.4)	4,171 (56.0)
Spermatocytic seminoma	14 (0.6)	31 (0.5)	40 (0.5)
Embryonal Ca	430 (18.9)	846 (15.4)	853 (11.4)
Malignant teratoma	373 (16.4)	1,203 (21.2)	1,659 (22.3)
Chorioca	118 (5.2)	210 (3.7)	184 (2.5)
Nongerm cell tumors	118 (5.2)	322 (5.7)	537 (7.2)
Unspecified	6 (0.4)	6 (0.1)	8 (0.1)
Totals	2,280 (100.0)	5,677 (100.0)	7,452 (100.0)
AJCC stage:*			
I	779 (64.2)	3,141 (65.0)	4,800 (73.4)
II	156 (12.9)	295 (6.1)	1,107 (16.9)
III	106 (8.9)	324 (6.7)	633 (9.7)
IV	170 (14.0)	1,069 (22.1)	Not available
Subtotal	1,213 (100.0)	4,829 (100.0)	6,540 (100.0)
Unknown	1,067 (46.8)	848 (14.9)	912 (12.2)
Totals	2,280 (100.0)	5,677 (100.0)	7,452 (100.0)

* According to the AJCC *Manual for Staging of Cancer*, 2nd (1985 to 1986), 3rd (1990 to 1991) and 4th (1995 to 1996) editions.

TABLE 5. *Five-year relative survival for testicular cancer by race/ethnicity, diagnosis year, stage and age*

	All Males			White Males			Black Males	
	All	Younger Than 50	50 or Older	All	Younger Than 50	50 or Older	All	Younger Than 50
Diagnosis yr:								
1960–1963	Not available	Not available	Not available	63.0	Not available	Not available	Not available	Not available
1970–1973	Not available	Not available	Not available	72.0	Not available	Not available	Not available	Not available
1974–1976	78.7	78.1	82.9	78.8	78.2	83.3	75.9*	—
1977–1979	87.5	88.6	77.1	87.9	89.0	78.1	66.2*	—
1980–1982	91.9	91.9	91.8	92.1	92.0	92.7	89.7*	89.2*
1983–1985	91.0	91.8	82.3	91.3	92.3	80.7	87.9*	84.3*
1986–1988	95.2	95.3	93.5	95.7	95.7 95.8	94.4	—	—
1989–1991	95.4	95.5	93.8	95.9	95.8	94.8	89.8*	93.6*
1992–1994	95.4	95.7	90.4	95.6	95.9	60.1	85.2*	84.5*
1995–2000	96.9†	96.4†	88.3	96.2†	96.7†	89.4	87.3	90.4
1995–2000 All stages:	95.9	96.4	88.3	96.2	96.7	89.4	87.3	90.4
Localized	99.4	99.4	97.0	99.4	99.4	97.6	96.5*	99.6
Regional	95.9	96.4	89.9*	96.1	96.5	90.6*	Not available	Not available
Distant	71.8	75.1	38.7*	73.1	76.6	39.5*	Not available	Not available
Unstaged	89.1	91.6	Not available	90.2	93.0	Not available	Not available	Not available
1995–2000 Diagnosis age:								
Younger than 45	96.5	Not available	Not available	96.7	Not available	Not available	Not available	Not available
45–64	94.6	Not available	Not available	95.3	Not available	Not available	Not available	Not available
55–64	87.2	Not available	Not available	87.9	Not available	Not available	Not available	Not available
65–74	74.2*	Not available	Not available	75.9*	Not available	Not available	Not available	Not available
75 or Older	—	Not available	Not available	—	Not available	Not available	Not available	Not available
Younger than 65	96.1	Not available	Not available	96.4	Not available	Not available	Not available	Not available
65 or Older	73.9*	Not available	Not available	77.6*	Not available	Not available	Not available	Not available

Rates for 1960 to 1973 based on End Results data from a series of hospital registries and 1 population based registry, and rates for 1974 to 2000 from SEER 9 areas based on data from population based registries in Connecticut, Puerto Rico, Utah, Iowa, Hawaii, Atlanta, Detroit, Seattle-Puget Sound and San Francisco-Oakland, on patient followup into 2001 with no available data on black males 50 years or older (source: SEER Program [www.seer.cancer.gov] SEER*Stat Database: Incidence–SEER 9 Regs Public Use, November 2004 Sub [1973–2002], National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2005, based on the November 2004 submission).

* Survival rate SE between 5% and 10%.

† Statistically significant vs 1974 to 1976 ($p < 0.05$).

taining the current level of 95.9%. Table 5 shows 5-year relative survival rates by race, year of diagnosis, stage and age from the SEER database. Black men with testis cancer experienced a 5% decrease in survival rates between 1989 and 1991, and 1992 and 1994 from 89.8% to 85.2%. However, this was a temporary downturn and in the 1995 to 2000 data set the survival of black men increased to 87.3%. Survival rates are best for patients who present with localized disease. When stratified by stage at presentation, men diagnosed between 1995 and 2000 with localized disease had a survival rate of 99.4% compared with 95.9% and 71.8% for regional and distant disease, respectively. Men diagnosed at a younger age also had better survival rates. In the 1995 to 2000 cohort men younger than 50 years had a 5-year relative survival rate of 96.4% compared with 88.3% for men older than 50 years. Finally, men diagnosed more recently had better survival rates. A man diagnosed in 1995 had a 95.9% chance of 5-year survival, while the rate for a man diagnosed in 1974 was 78.7%. Men with seminoma had better survival rates than those with NSGCT. The 5-year survival rate for seminoma was 97.9% and that for NSGCT was 96.5%.

Mortality. Testis tumors are exceedingly curable and mortality is low. SEER data on 1997 to 2001 placed the age adjusted death rate from testis cancer for American men at 0.3/100,000 (table 6). The overall death rate from testicular germ cell tumors decreased by 71% between 1975 and 2001 from 0.7/100,000 to 0.2/100,000. During this period the death rate decreased from 0.8/100,000 to 0.3/100,000 for white men and from 0.4/100,000 to 0.2/100,000 for black men. These findings indicate that white males have a higher lifetime risk of dying from testis cancer than black males (0.02% vs 0.01%).

Changes in Treatment Approaches

Seminoma. The management of seminoma remained relatively consistent in the last decade. Approximately 75% of patients in the NCDB underwent radiotherapy after radical orchiectomy.[7] However, a growing proportion of patients with clinical stage I disease were being treated initially with surgery alone, representing an increase from 15.8% in 1985 to 1986, to 21% in 1995 to 1996, presumptively followed thereafter with surveillance.[5] The use of surgery and radiation remained stable at 76% in 1985 to 1986 and 74% in 1995 to 1996 during the period studied. As expected, the use of LND in seminoma was rare at 0.6%. Chemotherapy is becoming the standard treatment for advanced seminoma

TABLE 6. *Age adjusted death rates for testicular cancer in 1997 to 2001 by race/ethnicity*

Race/Ethnicity	1997–2001 Rate/100,000 Population	1992–2001 Annual % Change Trend
All	0.3	−1.3
White:	0.3	−1.4
Hispanic	0.2	−4.0
NonHispanic	0.3	−0.8
Black	0.2	2.3
Hispanic	0.2	−3.9

Data from public use file provided by the National Center for Health Statistics, Hispanic and nonHispanic data not mutually exclusive from Whites, Blacks, Asian/Pacific Islanders, and American Indians/Alaska natives data, Hispanic and nonHispanic incidence data do not include Detroit, Hawaii and Alaska Native Registry, and no available data on Asian/Pacific Islander or North American native/Alaska native (source: SEER Program [www.seer.cancer.gov] SEER*Stat Database: Incidence–SEER 9 Regs Public Use, November 2004 Sub (1973–2002). National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2005, based on the November 2004 submission).

after orchiectomy. Its rate of use increased from 25.7% in 1985 to 1986, to 51.5% in 1995 to 1996.[7] Consequently the rate of use of radiotherapy for higher stage disease decreased from 43.3% in 1985 to 1986, to 27.2% in 1995 to 1996.[5] These results may reflect in part the increasing use of single dose carboplatin for stage I seminoma.

NSGCT. For patients with early stage NSGCT NCDB data revealed an increase in the use of surgery as a single modality therapy from 69.8% in 1985 to 1986, to 75% in 1995 to 1996. While the use of retroperitoneal LND increased from 12.6% in 1985 to 1986, to 17.6% in 1995 to 1996, so did orchiectomy as single therapy from 18.3% in 1985 to 1986, to 45% in 1995 to 1996, again reflecting the use of surveillance as primary treatment, followed by salvage therapy if necessary.[5] The rate of use of chemotherapy for early disease remained relatively stable at 24%. However, its rate of use for advanced NSGCT increased from 75% in 1985 to 1986, to 87% in 1995 to 1996 (table 7).[5]

Trends in Health Care Resources and Use

Inpatient care. Patients with testis cancer may require inpatient hospitalization for surgery, chemotherapy or any of the potential side effects of either treatment. Orchiectomy rarely requires hospitalization. According to HCUP the rate of national inpatient hospitalizations for testis cancer as a primary diagnosis was 1.8/100,000 (2,230 admissions) in 1994 and 1.4/100,000 (1,907) in 2000 (table 8). The age adjusted hospitalization rate decreased slightly for white men and increased slightly for Hispanic men. No HCUP data were available on black men with testis cancer.

Hospitalization rates were highest in the 25 to 34-year-old age group, followed by the 18 to 24, 35 to 44 and 45 to 54-year-old groups, reflecting the age distribution of men with testis cancer. Little geographic variation existed except in the Northeast, where hospitalization rates were almost double those of all other regions in 1994. Admission rates were highest in urban areas, most likely reflecting the treatment of many patients with testis cancer at tertiary care centers of excellence for complex surgery and chemotherapy.

Outpatient care. An individual with testis cancer may be seen in the outpatient setting during diagnosis, treatment and followup. This includes initial evaluation before and after orchiectomy, before and after any secondary surgeries, during radiation and chemotherapy, and during surveil-

TABLE 7. *Treatment modality by histological disease type and testicular cancer stage*[7]

	1985–1986		1990–1991		1995–1996	
	Early	Advanced	Early	Advanced	Early	Advanced
			Seminoma			
Surgery alone:						
Testicle excision without LND	4.7	1.4	13.9	3.3	16.8	4.4
Testicle excision with LND	3.7	1.4	1.0	1.4	0.6	0.7
Orchiectomy NOS	3.5	2.7	3.6	0.7	3.5	1.7
Surgery NOS	3.9	0.0	0.5	0.0	0.1	0.2
Surgery + radiation:						
Testicle excision without LND	25.3	18.9	67.4	15.6	61.2	20.4
Testicle excision with LND	12.0	8.1	2.2	2.5	1.7	1.2
Orchiectomy NOS	17.2	9.5	12.4	5.8	11.1	4.9
Surgery NOS	20.9	6.8	1.1	1.1	0.1	0.7
Surgery + chemotherapy:						
Testicle excision without LND	0.5	10.8	1.7	30.1	1.2	38.4
Testicle excision with LND	0.5	5.4	0.3	4.3	0.1	4.1
Orchiectomy NOS	0.8	2.7	0.8	8.7	0.6	7.3
Surgery NOS	0.5	6.8	0.1	2.9	0.0	1.7
Other treatment modalities	5.7	21.6	4.0	22.1	1.9	13.6
No treatment indicated	0.7	4.1	1.1	1.4	0.5	0.5
Totals	100	100	100	100	100	100
No. cases	593	74	2393	276	3391	411
			NSGCT			
Surgery alone:						
Testicle excision without LND	18.3	2.7	35.2	2.6	45.3	5.9
Testicle excision with LND	12.6	1.6	21.4	3.2	17.6	3.6
Orchiectomy NOS	13.3	2.1	9.2	2.1	9.5	1.6
Surgery NOS	25.6	5.3	2.4	1.3	2.4	0.8
Surgery + radiation:						
Testicle excision without LND	0.7	0.0	0.4	0.1	0.6	0.1
Testicle excision with LND	0.3	0.0	0.0	0.0	0.1	0.0
Orchiectomy NOS	0.3	0.0	0.1	0.0	0.1	0.0
Surgery NOS	0.3	0.0	0.0	0.1	0.0	0.0
Surgery + chemotherapy:						
Testicle excision without LND	5.6	28.3	13.6	38.4	15.0	45.6
Testicle excision with LND	5.6	14.4	6.5	20.6	2.8	17.9
Orchiectomy NOS	4.3	13.9	5.2	10.4	3.9	12.1
Surgery NOS	6.0	18.7	1.2	7.0	0.5	3.5
Other treatment modalities	1.7	11.8	4.0	13.4	1.8	8.5
No treatment indicated	3.3	1.1	0.9	0.8	0.5	0.4
Totals	100	100	100	100	100	100
No. cases	301	167	1207	719	1542	827

Early—1985 to 1986 AJCC stages I and II, 1990 to 1991 AJCC stages I to III, and 1995 to 1996 AJCC stages I and II N1, and advanced—1985 to 1986 AJCC stages III and IV, 1990 to 1991 AJCC stage IV, and 1995 to 1996 AJCC stages II (N2 or higher) and III according to the AJCC *Manual for Staging of Cancer*, 2nd (1985 to 1986), 3rd (1990 to 1991) and 4th (1995 to 1996) editions.

TABLE 8. *Inpatient hospital stays for testicular cancer as primary diagnosis*

	1994			1996			1998			2000		
	Count	Rate (95% CI)	Age Adjusted Rate	Count	Rate (95% CI)	Age Adjusted Rate	Count	Rate (95% CI)	Age Adjusted Rate	Count	Rate (95% CI)	Age Adjusted Rate
Totals	2,230	1.8 (1.6–2.0)	1.8	1,890	1.5 (1.3–1.7)	1.5	1,993	1.5 (0.9–2.2)	1.5	1,907	1.4 (1.2–1.6)	1.4
Age:*												
18–24	407	3.3 (2.4–4.2)		296	2.4 (1.7–3.1)		414	3.3 (1.5–5.1)		396	3.0 (2.2–3.8)	
25–34	951	4.7 (3.8–5.6)		771	3.9 (3.1–4.7)		732	3.8 (2.0–5.6)		647	3.5 (2.8–4.3)	
35–44	561	2.8 (2.3–3.4)		483	2.3 (1.8–2.8)		522	2.4 (1.4–3.4)		553	2.5 (2.0–3.1)	
45–54	158	1.1 (0.7–1.6)		†	†		†	†		151	0.8 (0.5–1.2)	
55–64	†	†		†	†		†	†		†	†	
Race/ethnicity:												
White	1,526	1.7 (1.4–1.9)	1.7	1,221	1.3 (1.1–1.5)	1.3	1,333	1.4 (0.6–2.2)	1.5	1,027	1.1 (0.9–1.3)	1.1
Hispanic	176	1.4 (0.8–1.8)	1.1	136	1.0 (0.5–1.4)	0.9	†	†	1.1	289	1.8 (1.0–2.5)	1.5
Region:												
Midwest	489	1.7 (1.2–2.1)	1.7	477	1.6 (1.2–2.0)	1.6	349	1.1 (0.7–1.6)	1.2	392	1.3 (0.9–1.6)	1.3
Northeast	586	2.8 (2.1–3.5)	2.8	345	1.4 (0.9–1.9)	1.4	†	†	3.0	334	1.4 (1.0–1.6)	1.4
South	579.0	1.4 (1.1–1.7)	1.4	610	1.4 (1.1–1.7)	1.4	455	1.0 (0.8–1.2)	1.0	575	1.2 (0.9–1.6)	1.2
West	475	1.7 (1.3–2.1)	1.7	458	1.6 (1.0–2.1)	1.5	443	1.5 (1.0–2.0)	1.4	606	2.0 (1.4–2.6)	2.0
Metropolitan statistical area:												
Rural	188	0.6 (0.4–0.8)	0.6	167	0.6 (0.4–0.9)	0.7	†	†	†	194	0.7 (0.4–0.9)	0.7
Urban	2,034	2.2 (1.9–2.5)	2.2	1,695	1.7 (1.4–2.0)	1.7	1,863	1.8 (1.0–2.7)	1.8	1,713	1.6 (1.4–1.9)	1.6

Rate per 100,000 based on 1994, 1996, 1998 and 2000 population estimates from CPS, CPS Utilities, Unicon Research Corp., for relevant demographic categories of male civilian noninstitutionalized population in the United States, age adjusted rate adjusted to the United States Census derived age distribution of the year under analysis and individuals of other races, and with missing or unavailable race and ethnicity, and missing metropolitan statistical area included in the total (counts may not sum to total due to rounding) (source: HCUP Nationwide Inpatient Sample, 1994, 1996, 1998 and 2000).

* Values for younger than 18, and 65 to 85 years or older do not meet reliability or precision standard.

† Value does not meet reliability or precision standard.

lance for recurrence. Emergency room visits are exceedingly rare and consequently there is insufficient information on which to base any conclusions.

Physician office visits. In Centers for Medicare and Medicaid Services data for 1992, 1995, 1998 and 2001 physician office visit rates increased significantly from 1992 to 1998 and then remained stable for men younger than 65 years (table 9). For men older than 65 years the age adjusted rate varied minimally from 1992 to 2001. Variability was seen across geographic regions and racial/ethnic strata. Greater reliance on outpatient care resulted not surprisingly in increased physician office visits, corresponding to the decrease in inpatient hospitalizations (table 8). Data on physician office visits by black and Hispanic men are difficult to interpret due to small sample size, and low counts preclude drawing firm conclusions regarding trends. However, for black men the rates of physician office visits decreased steadily from 1992 to 2001 (with an exception in 1998) with an overall ultimate decrease of 50%. A similar trend was seen in Hispanic men, for whom the number of physician office visits almost tripled from 1995 to 1998 and then subsequently decreased by 40%.

Hospital outpatient visits. In Centers for Medicare and Medicaid Services data on 1992, 1995, 1998 and 2001 age adjusted outpatient hospital visit rates decreased consistently from 1992 to 1998 before rebounding slightly in 2001 for an overall 48% decrease (table 10). The decrease was most notable in men younger than 65 years (an 88% decrease). Outpatient visits from 1992 to 2001 decreased by 83% in the Midwest and Northeast, by 68% in the West and by 45% in the South. A decrease would be expected for men on surveillance and outpatient chemotherapy because these treatments are commonly performed in physician offices. In fact, table 11 shows that inpatient chemothorapy is decreasing. From 1994 to 2000 the rate of inpatient chemotherapy infusions decreased by 33%.

Economic Impact

According to data from the Ingenix data set for 2002 the estimated annual expenditure for privately insured individuals between ages 18 and 54 years with claims corresponding to a diagnosis of testis cancer was $9,953 (table 12). Of this amount $8,816 were for medical costs and $1,137 were for prescription medications. The annual expenditure for males 18 to 54 years old without a claim for testis cancer was $3,717. The difference of $6,236 after controlling for differences in age distribution, median household income, health insurance type and 28 comorbid conditions may be attributable to expenditures directly or indirectly related to testis cancer.

Men 45 to 54 years old had the highest annual expenditure at $7,343, although sample sizes were small (table 12). Moreover, this age group had an increase in medication costs, which were 70% greater than the mean medication costs for all age groups. This may reflect a greater use of chemotherapy in the older patient population, and a greater reliance on surgery and/or observation in younger patients. When stratified by region, costs were fairly consistent and they generally correlated with expenditures of men without testis cancer (table 12).

National estimates of annual medical expenditures placed the total cost of treating testis cancer at $21.8 million in 2000 exclusive of medications, representing a 10% increase over the total in 1994 (table 13). Between 1994 and 2000 the percent of total costs attributable to hospital outpatient costs remained stable at 7.7% to 8.7%, the percent of ambulatory surgery costs remained stable at 14.9% to 16.8% and inpatient costs decreased slightly from 77.4% to 74.6%. This reflects the trend of care being transferred to the office and outpatient settings.

TABLE 9. *Physician office visits by Medicare beneficiaries with testicular cancer as primary diagnosis*

	1992			1995			1998			2001		
	Count	Rate (95% CI)	Age Adjusted Rate	Count	Rate (95% CI)	Age Adjusted Rate	Count	Rate (95% CI)	Age Adjusted Rate	Count	Rate (95% CI)	Age Adjusted Rate
Totals	4,360	29 (25–33)		6,080	40 (35–44)		5,940	41 (35–46)		5,240	40 (35–45)	
Total younger than 65	1,840	69 (47–71)		2,440	71 (58–83)		2,920	65 (71–99)		3,180	84 (71–97)	
Total 65 or older	2,529	21 (19–25)	23	3,640	31 (26–35)	31	3,020	27 (25–32)	27	3,060	25 (22–31)	26
Age:												
65–69	660	16 (11–22)		1,440	37 (29–46)		680	20 (13–27)		1,240	35 (26–44)	
70–74	520	16 (9.8–22)		640	19 (13–26)		1,200	39 (29–49)		720	23 (16–31)	
75–79	740	33 (22–43)		1,000	44 (32–56)		520	23 (14–32)		700	29 (19–38)	
80–84	200	15 (5.8–25)		260	19 (6.6–29)		280	20 (9.7–31)		120	8.0 (1.6–14)	
85–89	160	27 (8.2–46)		100	16 (1.9–30)		340	62 (27–77)		120	17 (3.3–30)	
90–94	240	118 (51–186)		180	85 (29–141)		0			160	69 (21–117)	
95–97	0			20	53 (0.0–156)		0			0		
98 or Older	0			0			0			0		
Race/ethnicity:												
White	3,840	31 (26–35)	20	5,900	43 (36–46)	41	5,400	44 (39–49)	44	5,620	43 (38–48)	43
Black	280	22 (10–33)	24	300	22 (11–33)	16	320	24 (12–36)	25	160	12 (4.2–20)	12
Asian	Not available	Not available	Not available	0			0			0		
Hispanic	Not available	Not available	Not available	40	20 (0.0–46)	20	160	48 (15–81)	54	120	32 (6.4–58)	32
North American native	Not available	Not available	Not available	0			0			40	120 (0.0–265)	120
Region:												
Midwest	860	23 (16–30)	25	1,700	44 (35–53)	43	1,440	39 (30–48)	40	1,340	35 (27–44)	37
Northeast	1,700	54 (42–65)	48	880	28 (19–36)	26	820	30 (20–39)	29	1,780	61 (48–74)	60
South	1,360	28 (20–32)	27	1,960	36 (29–43)	34	2,480	46 (38–54)	49	2,540	44 (36–51)	42
West	440	18 (11–26)	19	1,520	66 (51–80)	75	1,140	51 (38–64)	43	560	23 (15–32)	23

Unweighted counts multiplied by 20 to arrive at values; rate per 100,000 male Medicare beneficiaries in the same demographic stratum, age adjusted rate adjusted to the 2000 United States Census and individuals of other races, unknown race and ethnicity, and other region included in the total (counts less than 600 should be interpreted with caution) (source: Centers for Medicare and Medicaid Services, 5% Carrier and Outpatient Files, 1992, 1995, 1998 and 2001).

TABLE 10. *Hospital outpatient visits by Medicare beneficiaries with testicular cancer as primary diagnosis*

	1992			1995			1998			2001		
	Count	Rate (95% CI)	Age Adjusted Rate	Count	Rate (95% CI)	Age Adjusted Rate	Count	Rate (95% CI)	Age Adjusted Rate	Count	Rate (95% CI)	Age Adjusted Rate
Total	1,800	12 (9.6–15)		820	5.4 (3.7–7.0)		1,060	7.3 (5.4–9.3)		460	3.0 (1.8–4.2)	
Total younger than 65	1,320	42 (32–52)		520	15 (9.3–21)		900	26 (19–34)		200	5.3 (2.0–8.6)	
Total 65 or older	480	4.1 (2.4–5.7)	4.2	300	2.6 (1.3–3.9)	2.4	160	1.4 (0.4–2.5)	1.4	260	2.2 (1.0–3.5)	2.2
Age:												
65–69	100	2.5 (0.3–4.6)		180	4.7 (1.6–7.7)		80	2.4 (0.1–4.7)		120	3.4 (0.7–6.1)	
70–74	140	4.3 (1.1–7.5)		40	1.2 (0.0–2.8)		20	0.7 (0.0–1.9)		60	1.9 (0.0–4.2)	
75–79	160	7.1 (2.2–12)		60	2.6 (0.0–5.6)		60	2.6 (0.0–5.6)		80	3.3 (0.1–6.4)	
80–84	80	6.1 (0.2–12)		20	1.4 (0.0–4.2)		0			0		
85–89	0			0			0			0		
90–94	0			0			0			0		
95–97	0			0			0			0		
98 or Older	0			0			0			0		
Race/Ethnicity:												
White	1,660	13 (10–16)	13	740	5.7 (3.9–7.5)	5.5	900	7.4 (5.2–9.6)	7.4	380	2.9 (1.6–4.2)	2.9
Black	20	1.6 (0.0–4.6)	1.6	20	1.4 (0.0–4.3)	1.4	20	1.5 (0.0–4.4)	1.5	60	4.1 (0.0–8.7)	4.1
Asian	Not available	Not available	Not available	0			20	15 (0.0–43)	15	0		0.0
Hispanic	Not available	Not available	Not available	20	10 (0.0–30)	10	120	36 (7.2–64)	36	20	5.3 (0.0–16)	5.3
North American native	Not available	Not available	Not available	0			0			0		
Region:												
Midwest	680	18 (12–25)	19	440	11 (6.6–16)	10	180	4.9 (1.7–8.1)	4.9	120	3.2 (0.6–5.7)	3.2
Northeast	540	17 (11–23)	16	180	5.7 (1.8–9.4)	5.7	60	2.9 (0.1–5.7)	2.9	80	2.7 (0.1–5.4)	2.7
South	200	3.8 (1.5–6.2)	3.8	80	1.5 (0.0–2.9)	1.5	620	12 (7.9–16)	12	120	2.1 (0.4–3.7)	2.1
West	380	18 (8.7–23)	15	120	5.2 (1.0–9.3)	6.0	160	7.2 (2.2–12)	7.2	120	4.8 (1.0–8.7)	4.8

Unweighted counts multiplied by 20 to arrive at values, rate per 100,000 male Medicare beneficiaries in the same demographic stratum, age adjusted rates adjusted to the 2000 United States Census and individuals of other races, unknown race and ethnicity, and other region included in the total (counts less than 600 should be interpreted with caution) (source: Centers for Medicare and Medicaid Services, 5% Carrier and Outpatient Files, 1992, 1995, 1998 and 2001).

TABLE 11. *Chemotherapy during inpatient hospital stays for testicular cancer as primary diagnosis rate*

	Count	Rate/100,000 Population (95% CI)	Rate/100,000 Visits for Condition (95% CI)
1994:			
Total	2,230	1.8 (1.6–2.0)	
Chemotherapy	384	0.3 (0.2–0.4)	16,323 (11,883–20,807)
1996:			
Total	1,890	1.5 (1.3–1.7)	
Chemotherapy	298	0.2 (0.2–0.3)	15,787 (11,376–20,159)
1998:			
Total	1,993	1.5 (0.9–2.2)	
Chemotherapy	336	0.3 (0.2–0.3)	16,859 (11,139–22,529)
2000:			
Total	1,907	1.4 (1.2–1.6)	
Chemotherapy	295	0.2 (0.2–0.3)	15,469 (10,388–20,656)

Rate per 100,000 based on 1994 to 2000 population estimates from CPS, CPS Utilities, Unicon Research Corp., for relevant demographic categories of male civilian noninstitutionalized population in the United States and rate per 100,000 male visits for testicular cancer in HCUP National Inpatient Sample, 1994 to 2000 (source: HCUP Nationwide Inpatient Sample, 1994, 1996, 1998 and 2000).

TABLE 13. *Testicular cancer expenditures by service site*

	$ Expenditures (%)
1994:	
Hospital outpt	1,521,508 (7.7)
Physician office	— (0.0)
Ambulatory surgery	2,941,777 (14.9)
Emergency room	— (0.0)
Inpt	15,300,472 (77.4)
Total	19,763,756
1996:	
Hospital outpt	1,638,654 (8.7)
Physician office	— (0.0)
Ambulatory surgery	3,168,275 (16.9)
Emergency room	— (0.0)
Inpt	13,966,091 (74.4)
Total	18,773,020
1998:	
Hospital outpt	1,740,460 (8.4)
Physician office	— (0.0)
Ambulatory surgery	3,365,113 (16.2)
Emergency room	— (0.0)
Inpt	15,642,173 (75.4)
Total	20,747,745
2000:	
Hospital outpt	1,885,496 (8.7)
Physician office	— (0.0)
Ambulatory surgery	3,645,539 (16.8)
Emergency room	— (0.0)
Inpt	16,214,464 (74.6)
Total	21,745,500

Source: National Ambulatory and Medical Care Survey, National Hospital and Ambulatory Medical Care Survey, HCUP and Medical Expenditure Panel Survey, 1994, 1996, 1998 and 2000.

Testis cancer is rare in prepubertal males. However, data from the National Association of Children's Hospitals and Related Institutions database indicated that the mean inpatient cost per child with testis cancer listed as a primary diagnosis was $21,892 in 2001, representing a 2.3-fold increase over the cost in 1999 (table 14). In summary data from 1999 to 2001 increases in costs correlated directly with increases in age. Males 11 years or older with a primary diagnosis of testis cancer had costs that were almost 3 times greater than those for patients 10 years or younger. This may be because older children admitted to inpatient facilities had a higher proportion of recurrent cancers involving more intensive care, while younger patients were admitted for the initial cancer procedure.

Marketscan Health and Productivity Management data on 1999 allowed assessment of the impact of a diagnosis of testis cancer on employment (table 15). Most men with testis cancer were in the age range when they would be enrolled in school or employed. Marketscan Health and Productivity Management data indicated that 16% of men with testis cancer missed work for treatment of the disease. An average of 0.7 hours of work was missed for inpatient hospitalization and 7.7 hours were missed for outpatient visits. Hence, the average total hours of work missed was 8.4. This suggests that most men with testis cancer were under surveillance or underwent primary treatment before 1999, of which either would result in only occasional followup visits to a physician office.

DISCUSSION

Testis cancer is relatively uncommon, representing less than 1% of all male malignancies. Still, it is currently the most common cancer in men 20 to 34 years old. Although the incidence of testis cancer in the United States contin-

TABLE 12. *Estimated annual expenditures of privately insured employees with and without testicular cancer medical claim in 2002*

	$ Annual Expenditures/Pt Ages 18–64 Without Testicular Ca (285,095 men)			$ Annual Expenditures/Pt Ages 18–64 With Testicular Ca (236 men)		
	Medical	Prescription Drugs	Totals	Medical	Prescription Drugs	Totals
All						
Age:	2,682	1,035	3,717	8,816	1,137	9,953
18–34	1,288	654	1,942	6,905	875	7,780
35–44	2,149	875	3,024	8,443	1,193	7,636
45–54	3,067	1,211	4,278	9,660	1,941	11,621
Region:						
Midwest	2,584	1,022	3,606	8,492	1,126	9,618
Northeast	2,611	1,122	3,733	8,580	1,232	9,812
South	2,747	969	3,716	9,029	1,057	10,086
West	2,920	1,058	3,978	9,596	1,174	10,770

Primary beneficiaries 18 to 64 years old with employer provided insurance who were continuously enrolled in 2002, estimated annual expenditures derived from multivariate models controlled for age, gender, work status (active/retired), median household income based on zip code, urban/rural residence and medical and drug plan characteristics (managed care, deductible and co-insurance/co-payments) and binary indicators for 28 chronic disease conditions with predicted expenditures for ages 55 to 64 years omitted due to small sample size (source: Ingenix, 2002).

TABLE 14. *Annual work loss of males treated for testicular cancer*

	No. Workers (% missing work)	Av Hrs Work Absence (range)		
		Inpt	Outpt	Totals
Totals	45 (16)	0.7 (0–2.1)	7.7 (0–19.5)	8.4 (0–20.3)
Age:				
18–29	5 (0)	0	0	0
30–39	16 (19)	2 (0–6.3)	0.8 (0–1.9)	2.8 (0–7.1)
40–49	18 (17)	0	18 (0–48.6)	17.9 (0–48.6)
50–64	6 (17)	0	1.8 (0–6.5)	1.8 (0–6.5)
Region:				
Northeast	4 (0)	0	0	0
North Central	15 (13)	0	1.3 (0–3.1)	1.3 (0–3.1)
South	18 (17)	1.8 (0–5.5)	2.9 (0–6.5)	4.7 (0–11.2)
West	5 (40)	0	55 (0–198.3)	54.7 (0–198.3)
Unknown	3 (0)	0	0	0

Individuals with an inpatient or outpatient claim for testicular cancer and for whom absence data were collected, work loss based on reported absences contiguous to the admission or discharge dates of each hospitalization, or the date of the outpatient visit, and inpatient and outpatient including absences that started or stopped the day before or after a visit (source: Marketscan Health and Productivity Management, 1999).

ues to increase, the rate of increase is slowing. The reasons for this are unknown, although there is speculation that an increase in environmental endocrine disruptions may have a role.[8] No formal testis cancer prevention programs exist, so that there is no obvious explanation for this decrease. It is possible that the decrease is the indirect result of changes in behavior that influence risk factors, most specifically programs directed at preventing trauma and at awareness of the hazards of maternal hormone exposure, although to our knowledge this has never been definitively studied. Moreover, testis cancer is being diagnosed at an earlier age. This shift may reflect improved physician education, a greater emphasis on making young and adolescent boys more aware of their health issues and the dissemination of self-examination programs. However, the lack of stage migration at diagnosis casts doubt on the success of self-examination programs.

It has long been known that there is a disparity in the incidence and prevalence of testis cancer between white and black men in the United States. It is unclear whether this represents a sampling bias or a true biological and genetic difference. When changes in the incidence of testicular germ cell tumors in white and black men are stratified by histological subtypes, seminoma and nonseminoma have distinguishable incidence patterns in white and black racial groups.[5] The divergent trends in the incidence of seminoma and NSGCT may be the result of changes in underlying risk factors and etiological causes, alterations in biology, refinements in histological evaluation or changes in diagnostic practices, including coding practices.

White males have a higher lifetime risk of dying from testis cancer than black males (0.02% vs 0.01%). From 1992 to 2001 the annual mortality rate for white men decreased by 1.3%. While the annual mortality rate for black men was lower than that for white men, it increased by 2.3% between 1992 and 2001. No clear explanation for this divergence was apparent. It seems unlikely that the biology of testis cancer in black men has changed to make it more deadly. However, it is plausible that changes in epigenetic factors, such as diet or environmental exposure, could be worsening the prognosis. It is also possible that access to medical care or the treatment provided to black men deteriorated during the decade under study. In fact, 5-year relative survival rates for black men decreased between 1992 and 1994.

Biggs and Schwartz evaluated the relationship between survival and ethnicity in their examination of 16,086 cases from the SEER database between 1973 and 1999.[6] After multivariate analysis was performed to control for stage, histology and period of diagnosis black, Native American, Filipino and Hawaiian men were found to be at 2 to 3.5-fold greater risk for dying than nonHispanic white men. The risk of dying was 40% higher for

TABLE 15. *Annual work loss of males treated for testicular cancer*

	No. Workers (% missing work)	Av Hrs Work Absence (range)		
		Inpt	Outpt	Totals
Totals	45 (16)	0.7 (0–2.1)	7.7 (0–19.5)	8.4 (0–20.3)
Age:				
18–29	5 (0)	0	0	0
30–39	16 (19)	2 (0–6.3)	0.8 (0–1.9)	2.8 (0–7.1)
40–49	18 (17)	0	18 (0–48.6)	17.9 (0–48.6)
50–64	6 (17)	0	1.8 (0–6.5)	1.8 (0–6.5)
Region:				
Northeast	4 (0)	0	0	0
North Central	15 (13)	0	1.3 (0–3.1)	1.3 (0–3.1)
South	18 (17)	1.8 (0–5.5)	2.9 (0–6.5)	4.7 (0–11.2)
West	5 (40)	0	55 (0–198.3)	54.7 (0–198.3)
Unknown	3 (0)	0	0	0

Individuals with an inpatient or outpatient claim for testicular cancer and for whom absence data were collected, work loss based on reported absences contiguous to the admission or discharge dates of each hospitalization, or the date of the outpatient visit, and inpatient and outpatient including absences that started or stopped the day before or after a visit (source: Marketscan Health and Productivity Management, 1999).

Hispanic than for nonHispanic men. The investigators postulated that the observed disparities may reflect biological differences in the tumor, patient comorbidities or differences for which race is a proxy, including social, economic and health insurance status, treatment options and uptake, health care access and use, and environment, cultural and lifestyle factors.

Survival rates are best for patients who present with localized disease. From 1985 to 1991 the proportion of tumors presenting as stage I remained relatively stable, while the percent of stage II and III tumors decreased and stage IV tumors increased. This is an unexpected finding. With increased physician and patient education and awareness as well as self-examination programs one would expect stage migration, that is an increasing percent of localized tumors (stage I) coupled with decreasing rates of disseminated disease (stages II–IV). Several factors may explain these findings. Almost half of the patients in the NCDB had an unknown stage and this rate decreased to 12.2% by 1995 to 1996. In addition, considerable changes in staging practices occurred during the 11 years of data acquisition. However, when NCDB data were further divided into early and advanced disease, there still appeared to be little change in stage diatribution with time. These data confirm that more seminomas than NSGCTs are discovered earlier in the disease course. Interestingly in the SEER analysis men of Asian ancestry (China, Japan and the Philippines) had the highest incidence of localized disease, whereas Hawaiian men, who share some genetic heritage with this population, had the lowest incidence. This may reflect access to health care on the Hawaiian Islands as well as dietary and other environmental factors.

Men with seminomas have better survival rates than those with NSGCT. Although this may represent a difference in tumor biology and behavior between the 2 types of testis cancer, it may also result from the finding that men with seminoma generally present at an earlier stage.

Overall hospitalization rates for men with testis cancer decreased. This may reflect changes in treatment paradigms, including 1) improved surgical technique, 2) trends among surgeons to shorten postoperative hospital stay, 3) outpatient orchiectomy, 4) decreases in the number of chemotherapy cycles as primary treatment and the forgoing of some as adjuvant to retroperitoneal LND, 5) greater reliance on outpatient chemotherapy, 6) improved treatment and support of patients receiving chemotherapy and 7) increasing use of surveillance as a primary modality of treatment. Certain aspects of therapy are not covered in the available databases, such as the use of laparoscopy and changes in the dosing of chemotherapeutic agents. These are expected to have a profound effect in the next decade.

In white men, who are the majority of patients with testis cancer, care has clearly shifted to the outpatient setting. However, for black men the rates of hospitalization have not decreased as significantly and the rates of physician office visits also decreased steadily from 1992 to 2001 with an overall 50% ultimate decrease. A similar trend was seen in Hispanic men. This may reflect disparities in access to outpatient health care. Alternatively the high rates of hospitalization and low rates of outpatient visits by nonwhite men with testis cancer may reflect an unwillingness of physicians to use surveillance or outpatient chemotherapy for minority populations because of concerns about compliance or other factors. In addition, it is possible that nonwhite men are more comfortable receiving more aggressive, definitive and/or inpatient care, and they elect against outpatient treatment. Lastly, perhaps nonwhite men are presenting with more aggressive tumors that require greater amounts of in-hospital care and are associated with worse survival outcomes. Whatever the reason, this disparity requires further study.

White men experienced a 78% decrease in outpatient hospital visits. A decrease would be expected for men on surveillance and outpatient chemotherapy because these treatments are commonly performed in physician offices. Our data confirmed that inpatient chemotherapy is decreasing. From 1994 to 2000 the rate of inpatient chemotherapy infusions decreased by 33%.

Although inpatient hospitalization decreased, there was an increase in outpatient hospital visits by black men. Such an increase in hospital outpatient visits would also be expected if there was an increase in the number of men receiving radiotherapy. Hence, when data on outpatient hospital visits were combined with the inpatient hospital and physician office visit data presented, one could postulate that white patients with testis cancer are receiving increasing surveillance and in-office chemotherapy treatments, whereas nonwhite men are receiving less surveillance and more primary therapy, including radiation and procedures that require hospitalization, such as surgery and high dose chemotherapy.

Economic trends echoed the shifts from inpatient to outpatient care. While the total cost of treating testis cancer increased 10% between 1994 and 2000, inpatient costs decreased. Moreover, with more men being treated with surveillance and outpatient care the impact of testis cancer on the workplace seems limited.

CONCLUSIONS

The incidence of testis cancer in the United States continues to increase. However, the rate of increase is slowing. Fortunately testis tumors are exceedingly curable and their successful treatment represents a medical triumph and underscores the strength of multimodality therapy. Modifications in surgical technique and radiotherapy as well as improved methods of systemic chemotherapy have substantially decreased the morbidity of therapy. However, because of these successes, the treatment paradigms for testis cancer are changing. More patients are being treated with surveillance for early stage disease and care in general has shifted to the outpatient setting. With these changes there has been minimal standardization in treatment approaches. This as well as the relative rarity of testis cancer and subsequent limited database information makes evaluation for a project such as Urological Diseases in America difficult. There is a need to collect more comprehensive, detailed information, so that the burden of testis cancer on patients and the economy can be better evaluated.

Abbreviations and Acronyms

AJCC	=	American Joint Committee on Cancer
CPS	=	Current Population Survey
DCCPS	=	Division of Cancer Control and Population Sciences
HCUP	=	Healthcare Cost and Utilization Project
LND	=	lymphadenectomy
NCDB	=	National Cancer Data Base
NOS	=	not otherwise specified
NSGCT	=	nonseminomatous germ cell tumor
SEER	=	Surveillance, Epidemiology and End Results

REFERENCES

1. Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A et al: Cancer statistics, 2005. CA Cancer J Clin 2005; 55: 10.
2. Litwin MS, Saigal C, Yano EM, Avila C, Geschwind SA, Hanley JM et al: Urologic Diseases in America Project: analytical methods and principal findings. J Urol 2005; 173: 933.
3. Litwin MS and Saigal CS: Urologic Diseases in America Interim Compendium. Washington, D. C.: United States Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases 2004.
4. McKiernan JM, Goluboff ET, Liberson GL, Golden R and Fisch H: Rising risk of testicular cancer by birth cohort in the United States from 1973 to 1995. J Urol 1999; 162: 361.
5. McGlynn KA, Devesa SS, Sigurdson AJ, Brown LM, Tsao L and Tarone RE: Trends in the incidence of testicular germ cell tumors in the United States. Cancer 2003; 97: 63.
6. Biggs ML and Schwartz SM: Differences in testis cancer survival by race and ethnicity: a population-based study, 1973–1999 (United States). Cancer Causes Control 2004; 15: 437.
7. Steele GS, Richie JP, Stewart AK and Menck HR: The National Cancer Data Base report on patterns of care for testicular carcinoma, 1985–1996. Cancer 1999; 86: 2171.
8. Hardell L, Van Bavel B, Lindstrom G, Carlberg M, Eriksson M, Dreifaldt AC et al: Concentrations of polychlorinated biphenyls in blood and the risk for testicular cancer. Int J Androl 2004; 27: 282.

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Trends in testicular cancer incidence and mortality in 22 European countries: Continuing increases in incidence and declines in mortality

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This study profiles testicular cancer incidence and mortality across Europe, and the effects of age, period and generational influences, using age-period-cohort modeling. Despite a 5-fold variation in incidence rates, there were consistent mean increases in incidence in each of the 12 European countries studied, ranging from around 6% per annum (Spain and Slovenia) to 1–2% (Norway). In contrast, declines in testicular cancer mortality of 3–6% per annum were observed in the 1980s and 1990s for the majority of the 22 countries studied, particularly in Northern and Western Europe. The mortality trends in several European countries were rather stable (Romania and Bulgaria) or increasing (Portugal and Croatia). Short-term attenuations in increasing cohort-specific risk of incidence were indicated among men born between 1940 and 1945 in 7 European countries. In Switzerland, successive generations born from the mid 1960s may have experienced a steadily declining risk of disease occurrence. While the underlying risk factors responsible remain elusive, the temporal and geographical variability in incidence may point to an epidemic in different phases in different countries—the result of country-specific differences in the prevalence of one or several ubiquitous and highly prevalent environmental determinants of the disease. Advances in treatment have led to major declines in mortality in many European countries from the mid 1970s, which has translated to cohorts of men at successively lower risk of death from the disease. Slower progress in the delivery of optimal care is however evident from the mortality trends in several lower-resource countries in Southern and Eastern Europe. The first beneficiaries of therapy in these populations may be those men born—rather than diagnosed—in the era of major breakthrough in testicular cancer care.

Key words: testicular cancer; incidence; mortality; time trends; epidemiology

Testicular cancer accounts for 1–3% of all cancers in males in Western countries, but is the most common malignancy among young men (aged 15–34 years) in most European populations.[1] The highest incidence rates are recorded in a number of countries in Northern (Denmark, Norway), Central (Germany, Switzerland) and Eastern Europe (Czech Republic).[2] Incidence trends in almost all European populations are characterized by rapid increases in the last few decades,[2–7] particularly in adolescent men and young adults.[8]

The etiology of testicular cancer is not well understood, and the underlying reasons for the steadily increasing incidence trends throughout Europe are largely unknown. Improving ascertainment and better diagnostic procedures cannot account for the estimated 3–5% rises in incidence per annum, as the course of the disease is rapidly fatal if left untreated. In addition, the consistent evidence of uniformly rising secular trends comes from a number of well-established European cancer registries with standardized procedures.[4]

It has been hypothesized that the risk of testicular cancer is, to a large extent, determined very early in life, perhaps *in utero*.[9] Several perinatal factors, including low birth weight,[10–13] older maternal age,[12,14] prematurity,[10,11,14,15] low birth order,[10,12–14,16,17] have been associated with an increased risk of testicular cancer, although the evidence is not entirely consistent across studies. Testicular cancer is consistently associated with cryptorchidism, the most common congenital malformation of the male genital organs.[18] Results for perinatal risk factors have been often interpreted in the light of the so-called estrogen hypothesis, which postulates a carcinogenic effect of an excess of sex hormones at the time of testicular differentiation.[19] Maternal life-styles during pregnancy could also affect testicular cancer risk. In particular, ecologic studies have identified maternal smoking as a possible risk factor,[15] although this hypothesis has not found support from analytical studies.[20,21]

In contrast to incidence, testicular cancer mortality has been markedly declining in a number of European countries since the mid 1970s, because of the introduction of platinum-based chemotherapy schemes[22] and best-practice tumor management.[23] Echoing these improvements, the pooled 5-year relative survival estimate among European patients diagnosed in the early 1990s was over 90%, although striking differences across Europe were observed, with 5-year survival as low as 71% in Estonia.[24] The reductions in mortality have thus not been uniform between countries, with slower and later declines seen in lower resource settings,[25] in accordance with the high cost of appropriate treatments, or inadequate patient referral systems.[26]

To describe the impact of testicular cancer across Europe, our study systematically assesses the effects of age, period and generational influences on time trends of testicular germ-cell cancer incidence in 12 countries and testicular cancer mortality in 22 countries. We contrast country-specific temporal patterns of incidence in light of the putative and known risk factors for the disease, and mortality trends, with particular reference to the introduction of effective treatment practices.

Data sources and methods

Incidence

Incident cases of testicular germ-cell cancer (ICD-O-2 9060-9102) and corresponding population datasets were extracted from the EUROCIM software package and database[27] by registry, year

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TABLE I – TESTICULAR GERM CELL INCIDENCE: POPULATIONS INCLUDED IN THE TRENDS ANALYSIS, REGULAR TREND, AND GOODNESS-OF-FIT STATISTICS FOR BEST-FITTING APC MODEL BY EUROPEAN AREA

European area	Country	Period available (no. of 5-year periods)	Incident cases[1]	Male Person-years[2]	ASR[3]	Rank[4]	Overall trend 1993–97 (95% confidence interval)[5]	APC model[6]	Residual deviance[7]	d.f.[7]	*p*-value[7]
Northern	Denmark	1979–1998 (4)	263	1.5	16.7	1	1.9 (1.0–2.7)	AC	10.1	14	0.76
	Finland	1955–1999 (9)	61	1.5	4.2	11	2.9 (1.1–4.9)	APC	30.7	42	0.90
	Norway	1953–1997 (9)	155	1.3	11.9	3	1.1 (0.1–2.3)	APC	41.7	42	0.48
	Sweden	1964–1998 (7)	201	2.4	8.2	9	2.6 (1.6–3.7)	AC	33.7	35	0.53
	United Kingdom[8]	1978–1997 (4)	1359	15.1	8.6	8	2.6 (2.2–3.0)	AC	15.0	14	0.38
Eastern	Czech Republic	1985–1999 (3)	327	3.1	10.8	4	4.0 (3.1–4.9)	AC	7.3	7	0.40
	Slovakia	1968–1997 (6)	138	1.6	8.6	6	3.7 (2.4–5.1)	APC	28.0	24	0.26
Southern	Italy[9]	1983–1997 (3)	77	1.3	5.9	10	1.2 (−0.5–3.0)	A	16.1	16	0.45
	Slovenia	1985–1999 (3)	62	0.6	10.3	5	5.9 (3.6–8.4)	AD	15.4	15	0.42
	Spain[10]	1983–1997 (3)	31	0.9	3.2	12	5.9 (2.6–9.7)	AC	11.1	7	0.13
Western	France[11]	1978–1997 (4)	103	1.2	8.6	7	1.9 (0.5–3.4)	AC	6.4	14	0.96
	Switzerland[12]	1983–1997 (3)	140	0.8	15.9	2	1.2 (0.1–2.4)	AC	3.1	7	0.88

[1]Mean annual number of incidence cases 1993–97 in age group 15–54, except Czech Republic (1995–99).–[2]Mean annual male population 1993–97 in age group 15–54, except Czech Republic (1995–99), expressed in million person-years at risk.–[3]Truncated (ages 15–54) age standardised rate (TASR) 1993–97 (using European standard), except Czech Republic (1995–99).–[4]Ranked in descending order of TASR.–[5]Mean estimated annual percentage change based on the drift 1983–97 in age group 15–54, except Czech Republic (1985–99).–[6]The most parsimonious final model providing a good fit over the whole period available. A, Age; AD, Age + Drift; AC, Age + Drift + Cohort; AP, Age + Drift + Period; APC, Age + Drift + Period + Cohort.–[7]To determine the goodness-of-fit, the deviance was compared with the chi-squared distribution on the degrees of freedom (d.f.) determined by the model. A *p*-value of <0.05 denotes the full APC model does not yield an adequate fit.–[8]Aggregation of England, Scotland.–[9]Aggregation of Florence, Varese Province, Parma Province, Ragusa Province, Turin.–[10]Aggregation of Catalonia, Tarragona; Granada, Murcia, Navarra, Zaragoza.–[11]Aggregation of Bas-Rhin, Calvados, Doubs, Isere, Somme, Tarn.–[12]Aggregation of Basel, Geneva, Neuchatel, St.Gall-Appenzell, Vaud, Zurich.

of diagnosis and 5-year age group. A minimum requirement for a registry's inclusion in the analysis was their consecutive compilation in the last 3 volumes (6–8) of *Cancer Incidence in Five Continents* (CI5).[1,28,29] This criterion was chosen as a general marker of each registry's data quality over time, given the editorial process involves a detailed assessment of the comparability, completeness and validity of the submitted incidence datasets. In addition, each dataset was required to span a minimum of 15 years to enable the fit of age-period-cohort (APC) models to 5-year time periods and 5-year age groups. Because of the computation difficulties in dealing with small numbers, Estonia and Iceland were not included in the analyses.

Table I provides details of the cancer registries included in the analysis of incidence trends. In France, Spain, Italy and Switzerland, a number of regional registries were aggregated to obtain an estimate of the national incidence. As the span of data available from regional registries varied, the aggregation maximized the registration period, while ensuring as many of the regional registries were involved in the national estimation.

Mortality

Testicular cancer mortality data (ICD-9 186) were extracted from the WHO mortality databank by European country, year of death and 5-year age group (restricted again to men aged 15–54 years), alongside national population data from the same source. Two restrictions for inclusion were applied. First, as with incidence, datasets spanned at least 15 years, and second, the analysis was restricted to trends in mortality from 1968, in order to focus on how the effects of improving treatment, starting from 5 to 10 years later, subsequently impacted on the observed trends (see *Assumptions on period slopes for mortality*). Table II provides information on the national data from 22 countries that met the criteria: the time-span varied from 3–7 five-year periods. Because of their small numbers, Iceland, Luxembourg, Malta and Slovenia were not included in the subsequent analyses.

APC model

The incidence and mortality data were tabulated as birth cohorts in 10-year intervals by subtracting the midpoints of 5-year age groups (15–19, 20–24, . . . , 50–54) from the corresponding 5-year periods, with each resulting cohort overlapping by exactly 5 years. We assumed that the rates were constant within 5-year age classes $a = 1, 2, \ldots, A$ and 5-year periods of diagnosis $p = 1, 2, \ldots, P$, leading to a likelihood for the observations that is proportional to Poisson likelihood for the counts, with the log of the person-years of risk specified as an offset. The magnitude of the rates was described by a full APC model:

$$\log(\lambda(a,p)) = \alpha_a + \beta_p + \gamma_c$$

which can be fitted under the application of generalized linear model theory,[30] with the birth cohort derived from period and age such that $c = p - a$ for $c = 1, 2, \ldots, C$ with $C = A + P - 1$. The parameters α_a, β_p and γ_c refer to the fixed effects of age group a, period p and birth cohort c. The models were fitted using Stata 8.[31] Tests for the overall slope and separate effects of period and cohort curvature were obtained using the standard analysis of deviance of nested models, as suggested by Clayton and Schifflers.[32,33]

To allow a systematic evaluation of the trends across countries, the results are presented using the full APC model, and the non-identifiability problem was highlighted by partitioning the age, period and cohort effects in terms of their linear and curvature component parts, according to the method of Holford.[34,35] Holford showed that, while the overall slopes are unrestricted, they do not vary independently, given that the 3 linear slopes from an arbitrary APC model (indexed L) can be represented by $\alpha_L = \alpha_L + \rho_L$, $\beta_L = \beta_L - \rho$ and $\gamma_L = \gamma_L + \rho$, where α_L, β_L and γ_L are the true values for the slopes according to age, period and cohort, and ρ is an unknown constant that may result in increasing or decreasing trends of each slope.[34,35] The drift, the sum of the period and cohort slopes, $\beta_L + \gamma_L$, is therefore estimable[35] and used in this study to describe the overall direction and magnitude of the time trend in each country. For incidence, the recent drift was estimated on the basis of the most recent 15 years of data available; for mortality, the drift was obtained from the most recent 20-year period, in order to capture the full impact of the introduction of successful therapy (see *Assumptions on slopes for mortality*). To identify plausible period and cohort effects in the incidence and mortality trends, we postulated different specifications of the range of the period and cohort slopes, as outlined here.

TABLE II – TESTICULAR CANCER MORTALITY: POPULATIONS INCLUDED IN THE TRENDS ANALYSIS, REGULAR TREND AND GOODNESS-OF-FIT STATISTICS FOR BEST-FITTING APC MODEL BY EUROPEAN AREA

European area	Country	Period available (no. of 5-year periods)	Deaths[1]	Male Person-years[2]	ASR[3]	Rank[4]	Overall trend 1980-[5] (95% confidence interval)	APC[6] model	Residual[7] deviance	d.f.[7]	p-value[7]
Northern	Denmark	1969–1998 (6)	13	1.5	0.8	6	−3.4 (−5.8 to −0.6)	APC	31.4	30	0.40
	Finland	1970–1999 (6)	5	1.5	0.8	6	−4.0 (−6.5 to −1.1)	AP	39.2	42	0.59
	Ireland	1969–1998 (6)	4	1.0	0.8	6	−5.7 (−9.2 to −1.1)	AP	31.1	42	0.89
	Norway	1969–1998 (6)	6	1.3	0.6	7	−4.6 (−8.0 to −0.1)	AP	47.8	42	0.25
	Sweden	1969–1998 (6)	7	2.4	0.5	8	−5.1 (−8.1 to −1.3)	AP	40.1	42	0.55
	United Kingdom	1970–1999 (6)	68	16.5	0.5	8	−5.0 (−5.6 to −4.4)	APC	29.7	24	0.19
Eastern	Bulgaria	1970–1999 (6)	34	2.3	1.4	1	−0.1 (−1.4 to 1.2)	AP	35.5	35	0.45
	Czech republic	1986–2000 (3)	39	3.1	1.3	2	−3.0 (−4.5 to −1.4)	AC	8.7	7	0.27
	Hungary	1971–2000 (6)	34	2.9	1.2	3	−2.3 (−3.4 to −1.3)	AC	18.2	28	0.92
	Poland	1980–1994 (3)	114	10.7	1.0	4	−1.1 (−2.2 to 0.0)	AD	24.4	15	0.06
	Romania	1981–2000 (4)	48	6.5	0.9	5	−0.1 (−1.2 to 1.0)	A	29.7	24	0.19
Southern	Croatia	1986–2000 (3)	11	1.3	0.5	8	4.4 (−0.3 to 10.0)	A	13.0	16	0.68
	Greece	1969–1998 (6)	9	2.9	0.4	9	−2.9 (−5.9 to 0.8)	AC	33.2	28	0.23
	Italy	1969–1998 (6)	46	16.2	0.4	9	−4.0 (−5.3 to −2.6)	AP	55.2	42	0.08
	Portugal	1980–1999 (4)	11	2.8	0.4	9	2.0 (−0.7 to 5.1)	AC	22.7	14	0.06
	Spain	1974–1998 (5)	29	11.4	0.4	9	−0.9 (−3.0 to 1.4)	AD	42.0	31	0.09
Western	Austria	1971–2000 (6)	12	2.3	0.4	9	−4.5 (−5.9 to −2.9)	APC	29.8	30	0.48
	Belgium	1971–1995 (5)	7	2.8	0.3	10	−4.8 (−7.7 to −1.3)	AD	43.5	39	0.28
	France	1969–1998 (6)	78	16.4	0.3	10	−3.5 (−4.5 to −2.3)	AP	45.1	42	0.34
	Germany	1985–1999 (3)	148	23.2	0.3	10	−6.2 (−6.8 to −5.6)	APC	108.3	6	<0.01
	The Netherlands	1970–1999 (6)	22	4.7	0.3	10	−3.2 (−4.5 to −1.8)	APC	32.1	30	0.36
	Switzerland	1970–1994 (5)	17	2.0	0.2	11	−5.6 (−7.4 to −3.5)	AP	43.0	35	0.17

[1]Mean annual number of deaths in most recent 5-year period in age group 15–54.–[2]Mean annual male population in most recent 5-year period in age group 15–54, expressed in million person-years at risk.–[3]Truncated (ages 15–54) age standardised rate (TASR) in most recent 5-year period in age group 15–54 (using European standard).–[4]Ranked in descending order of TASR.–[5]Mean estimated annual percentage change based on the net drift in age group 15–54, in most recent two decades: Austria (1981–2000); Belgium (1981–1995); Bulgaria (1980–1999); Croatia (1986–2000); Czech Republic (1986–2000); Denmark (1984–1998); Finland (1980–1999); France (1984–1998); Germany (1985–1999); Greece (1984–1998); Hungary (1981–2000); Ireland (1984–1998); Italy (1984–1998); Norway (1984–1998); Poland (1982–1996); Portugal (1980–1999); Romania (1981–2000); Slovenia (1985–1999); Spain (1984–1998); Sweden (1984–1998); Switzerland (1980–1994); The Netherlands (1980–1999); United Kingdom (1980–1999); mean estimated annual percentage change based on the net drift in most recent 20-year period.–[6]Refers to the most parsimonious final model providing a good fit to the trends over the whole period available: A, Age; AD, Age + Drift; AC, Age + Drift + Cohort; AP, Age + Drift + Period; APC, Age + Drift + Period + Cohort.–[7]To determine the goodness-of-fit, the deviance was compared with the chi-squared distribution on the degrees of freedom (d.f.) determined by the model. A p-value of <0.05 denotes the full APC model does not yield an adequate fit.

Assumptions on incidence slopes

For incidence, we took into consideration both the possibility of period-specific increases, as would be expected in the event of improving diagnostic procedures or increasing ascertainment with time, and the importance of birth cohort influences, possibly due to the changing prevalence and distribution of known and putative risk factors that impact on cancer rates in successive generations. The substantial contribution of cohort influences in explaining testicular cancer incidence trends in Europe has been consistently demonstrated in previous reports,[3,6,36,37] and thus, we *a priori* assumed that the overall linear slopes of period and birth cohort were positive, and specified scenarios for which the cohort component accounted were (i) all of the regular trend, and (ii) half of the regular trend. The possible values of the cohort slopes (γ_L) were thus bounded so that $\frac{\beta_L+\gamma_L}{2} \leq \gamma_L \leq \beta_L + \gamma_L$, leaving the period slopes (β_L) to range between zero and half of the net drift defining the corresponding linear slopes as $0 \leq \beta_L \leq \frac{\beta_L+\gamma_L}{2}$. Age parameters were similarly bound between 2 estimable functions.

Assumptions on slopes for mortality

For mortality, we postulated 2 specifications for the period slope that mirror those for incidence. The first scenario attempted to capture the period-related declines in testicular cancer mortality due to the introduction of effective therapy and care starting in the early to mid 1970s, initially in high-resource European countries. The second specification took account that the regular trend is related to the underlying incidence (and its generational influences), as well as case-fatality. On the basis of these requirements, we present 2 sets of parameter estimates that constrain the period component β_L to take either:(i) all of the regular trend or (ii) half of the regular trend. The boundary values of the period slopes were $\frac{\beta_L+\gamma_L}{2} \leq \beta_L \leq \beta_L + \gamma_L$, and accordingly, the range of linear slopes for cohort γ_L were $0 \leq \gamma_L \leq \frac{\beta_L+\gamma_L}{2}$.

Each postulation of the period slope provided an identifiable range of the age and cohort slopes. The effects for the individual categories of each effect were generated by adding together the linear and curvature components. For example, the ath age effect can be expressed as $\alpha_a = (a - (A + 1)/2) \times \alpha_L + \varphi_a$, with φ_a representing the departures from the linear trend, and β_L and γ_L, the slopes for period and cohort, defined in the same way.[35]

Results

Background risk, age-adjusted trends and recent drift: incidence

During the most recent 5-year period available, there was a five-fold variation in incidence in the 12 European countries (in Table I), with rates ranging from around 3 per 100,000 in Spain through to more than 15 per 100,000 in Denmark and Switzerland. Increases in incidence during the period 1983–1997 were observed in all countries studied. The extent of the increase varied considerably, although no clear relation between the level of incidence and the magnitude of the recent trend was apparent (Fig. 1). The average increases per annum varied at least 6-fold (Table I), with the most rapid inclines in Spain and Slovenia, estimated to be almost 6% per year on average, compared with overall increases of 1–2% per annum in Norway, Switzerland, Italy, France and Denmark. There was a suggestion of a recent peak in several countries, most evidently in Switzerland and Norway, during the 1990s.

Background risk, age-adjusted trends and recent drift: mortality

The ratio of testicular cancer incidence to mortality ranged from 8:1 in the Czech Republic to over 30:1 in Switzerland, with a clus-

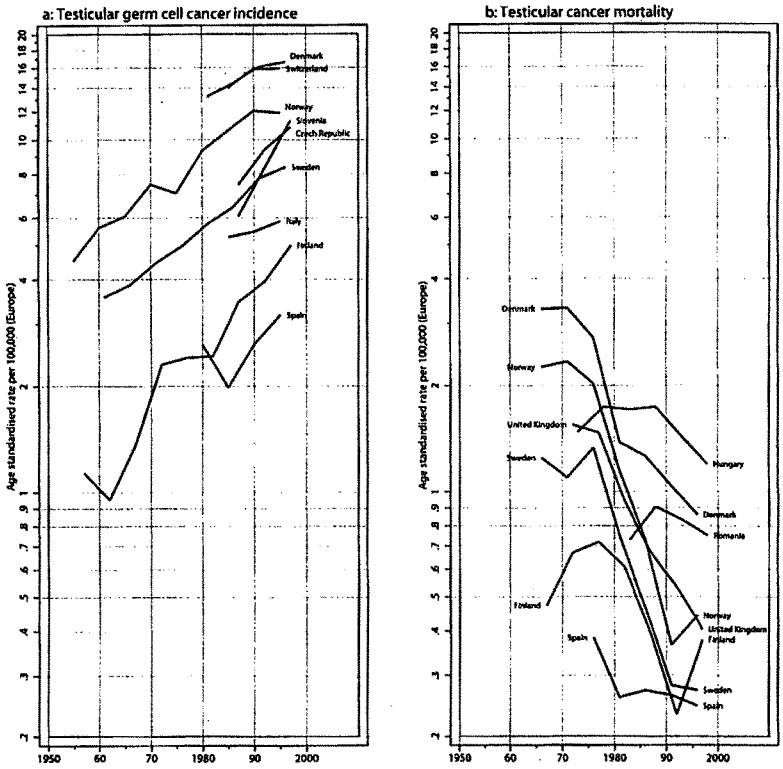

FIGURE 1 – Trends in truncated age-standardized (15–54 years) incidence and mortality rates (European standard) for selected countries. Rates are based on 5-year aggregates and corresponding to the period available, as described in Table I.

tering of rates within region more apparent than that was noted for incidence (Table II). Death rates in the most recent 5-year period were generally highest in Eastern Europe, with Bulgaria, the Czech Republic, Hungary, Poland and Romania holding the top 5 positions, with high-risk Denmark in sixth place (Table II). In further contrast to incidence, decreases in testicular cancer mortality were observed in 19 of the 22 populations in the most recent 2 decades (Fig. 1), with declines of 3–6% seen throughout Northern and Western Europe, as well as in Italy and the Czech Republic. Elsewhere in Eastern Europe (e.g. in Romania and Bulgaria), the magnitude of the declines were negligible (Table II), while in the South, nonsignificant increases in the overall mortality trend of 2% and over 4% were observed in Portugal and Croatia, respectively (Table II).

The declines in mortality rates started first in Denmark, Norway and the U.K in the 1970s, followed, a few years later, in Sweden, Finland and France. The lower level of recent mortality declines in Eastern Europe partially reflects a tendency for their respective downturns to have occurred mainly in the last decade of observation, from the late 1980s.

APC modeling

Incidence trends related to period and birth cohort. The full APC model or a submodel explained a sufficient amount of variation in each population (Table I). Cohort effects dominated in the majority, with cohort curvature significantly improving the fit in 10 of the 12 countries studied, with Italy and Slovenia being the exceptions (Table III). The age-cohort model adequately explained the variation in 7 countries (Table I). Only in 3 countries (Finland, Norway and Slovakia) did non-linear period effects significantly improve the fit (Table III).

Figure 2 shows the corresponding period and cohort risk parameters. It is evident that, even when half of the regular trend is attributed to the period of diagnosis, successive generational increases in risk can be seen in almost all European countries. The

TABLE III – PERIOD AND COHORT CURVATURE OVER AND ABOVE NET DRIFT (INCIDENCE)

European Area	Country	Period curvature			Cohort curvature		
		Δ Deviance[1]	Δ d.f.[2]	*p*-value[3]	Δ Deviance[1]	Δ d.f.[2]	*p*-value[3]
Northern	Denmark	1.7	2	0.43	30.0	9	<0.01
	Finland	16.8	7	0.02	33.1	14	<0.01
	Norway	18.4	7	0.01	57.8	14	<0.01
	Sweden	2.8	5	0.72	52.1	12	<0.01
	United Kingdom	2.4	2	0.30	22.2	9	0.01
Eastern	Czech Republic	1.3	1	0.25	39.4	8	<0.01
	Slovakia	27.5	4	<0.01	35.7	11	<0.01
Southern	Italy	0.2	1	0.69	12.2	8	0.14
	Slovenia	0.01	1	0.94	9.9	8	0.27
	Spain	1.7	1	0.20	16.1	8	0.04
Western	France	0.4	2	0.83	19.9	9	0.02
	Switzerland	1.8	1	0.18	29.5	8	<0.01

[1]The difference in the deviance of the Age + Drift model and the model with the non-linear effects of Period or Cohort added.–[2]The difference in the degrees of freedom of the Age + Drift model and the model with the non-linear effects of Period or Cohort added.–[3]To determine the statistical significance of the non-linear effect, the change in deviance was compared with the chi-squared distribution on the change in degrees of freedom between the models.

rises were fairly uniform and rapid with successive generations in Finland and the U.K. and in the Czech Republic and Slovakia.

There was some evidence of a short-term dip in cohort-specific risk (regardless of the attribution of drift) in most other European countries, followed by rapid accelerations in risk thereafter. This was seen most evidently in men born around 1940–1945 in Denmark, Norway, and possibly, Sweden, and also in France, Italy, Slovenia and Spain, although the data are based on fewer years of observation for these countries. There was also a suggestion that successive generations of Swiss men, born after the early to mid 1960s, may have experienced some declines in risk of testicular germ-cell cancer.

Mortality trends related to period and birth cohort. A deviance analysis of the mortality trends (Table II) indicates that the submodels or the full APC model provided an adequate fit in every country, excepting Germany. Period and cohort curvature significantly improved the fit in 14 and 13 populations, respectively (Table IV). Downward trends in mortality rates were seen in most Northern and Western European countries (and Italy) from the mid 1970s onward, translating (in spite of the rapid increases in incidence observed) to generation-specific decreases in risk of death for men born after 1940 (Fig. 3).

The period-specific trends elsewhere in Southern Europe are difficult to interpret. The reduction in risk by calendar period in Greece and Spain since the 1970s has led to a discontinuation in the increases in risk of death, amongst affected birth cohorts. In contrast, the risk of death appears to have increased in Portugal and Croatia in consecutive cohorts born after 1950. In Eastern Europe, period-specific declines are most evident in Hungary (where a sufficient span of data is available) and the Czech Republic. The declines in Bulgaria and Romania are seen at least a decade later than in Northern Europe, with cohort-specific declines suggested only in the latter country, and only among generations born recently.

Discussion

This study describes the temporal patterns of testicular germ-cell cancer incidence and testicular cancer mortality in European countries, with particular reference to the importance of cohort influence (on incidence) and period effects (on mortality). Similar multicountry analyses of incidence in Europe have been compiled previously,[5,6] although this report extends the analysis to 12 countries, including several in Southern and Eastern Europe. The variability in the geographical and temporal patterns within Europe is extensive: a 5-fold variation in incidence rates was observed, and there was a steady rise in incidence across populations that varied from 1 to 6% per annum. Rates rose most rapidly in low-risk Spain and intermediate-risk Slovenia, with Switzerland being the exception to the increasing profile, for which rates have been extremely high but stable over several decades,[38] with recent declines additionally suggested in this study. It can be speculated that a leveling off of incidence in high-risk countries may represent a mature phase in the epidemic, relative to lower-risk countries for which this phenomenon might be considered to be at an early phase, with further increases anticipated in forthcoming years.

Attention was first drawn to the increases in testicular cancer occurrence in England and Wales[39] and Denmark[40] half a century ago, yet the underlying causes are still largely unknown. The large variation in testicular cancer incidence both across the European countries and within each population over time could point to one or several ubiquitous and highly prevalent environmental agents being responsible, and moreover, must vary in prevalence according to population.

Regardless of temporal and geographical disparities, the age-incidence curves of testicular cancer are well-known to be largely invariate, implying that the age window of susceptibility to strong determinants of testicular cancer is likely equivalent in different populations.[9] One of the strongest lines of evidence relates to the importance of factors acting prenatally or early in life that may initiate the process of testicular carcinogenesis. The strong causes involved in the development of carcinoma *in situ*, the precursor lesion of all germ-cell tumors,[41] appear identical to the strong causes of testicular cancer.[9] Carcinoma *in situ* most probably occurs during the first trimester of pregnancy,[9] and the associations between testicular cancer and genital malformations and prenatal factors suggest that the strong causes of carcinoma *in situ* and, subsequently, of testicular cancer act prenatally. Increased estrogen exposure *in utero* has been related to increasing abnormities in the development and functioning of the testis,[19] and a number of prenatal and perinatal exposure-related factors have been implicated for testicular cancer in analytical studies.

Aside from congenital malformations, of which cryptorchidism is the strongest and the most consistent determinant,[18,32,43] certain prenatal factors have been reported in epidemiological studies with some consistency. These include premature birth,[10,11,14,15] low birth-weight,[10–14] high birth-weight,[10,13] neonatal jaundice,[11] exogenous estrogen use,[11,15] older maternal age[12,42] and first born.[10,12–14,16] Other factors that have been reported are smoking during pregnancy,[20,21] subfertility,[43,44] exposure to viral infections[45] and sedentary lifestyle.[43]

As has been consistently demonstrated,[3,6,7,37] generational influences appear largely responsible for the increasing incidence trends in Europe. Cohort curvature significantly improved the fit in all countries, except Italy and Slovenia, where age and age-drift

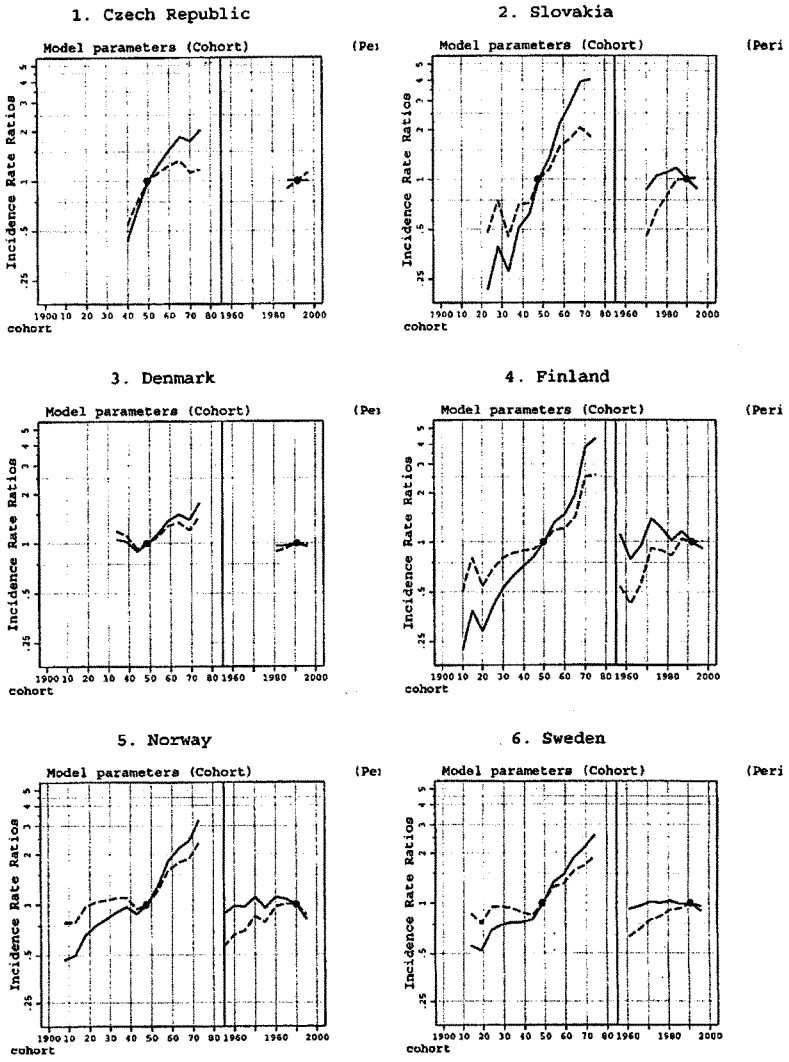

FIGURE 2 – Age period cohort parameters based on assumptions on period and cohort slopes: incidence trends by country within European area (Panels 1–5: E Europe; 6–11: N Europe; 12–16: S Europe; 17–22: W Europe). Solid line: assumption of zero period slope (drift taken up entirely by cohort); dashed line: assumption of equal and same-direction slopes for period and cohort (drift attributed equally to period and cohort).

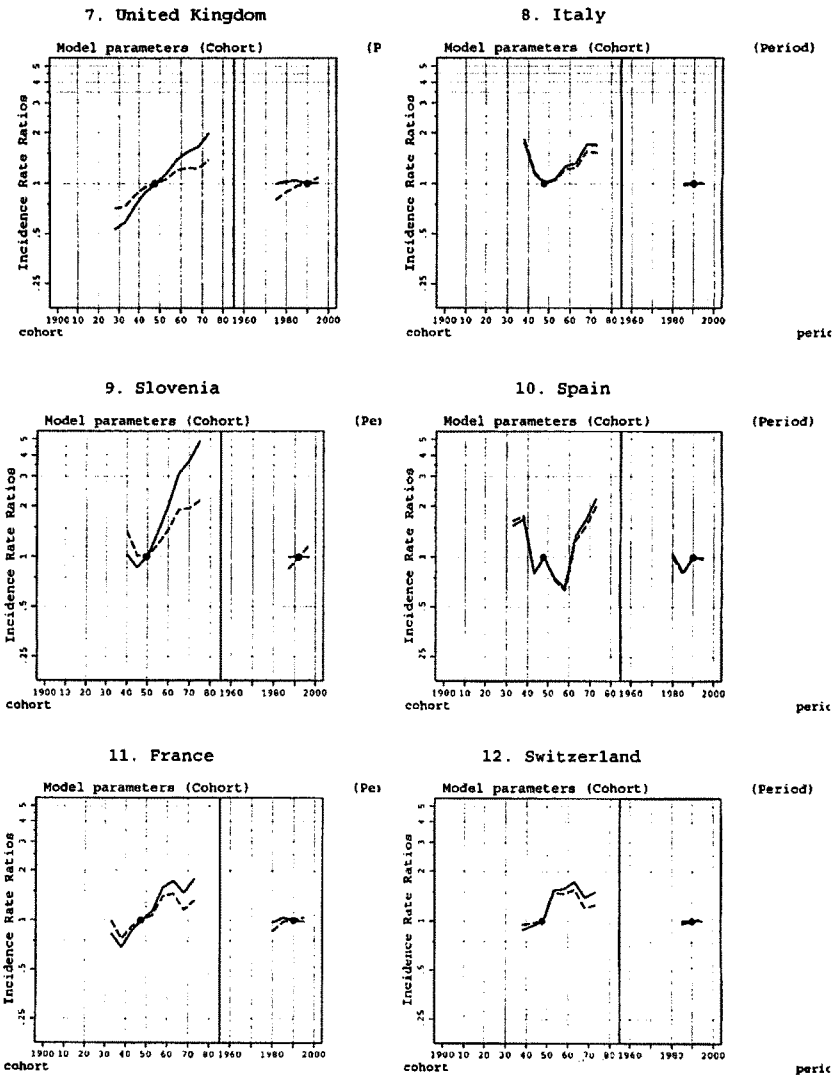

FIGURE 2 – CONTINUED.

TABLE IV – PERIOD AND COHORT CURVATURE OVER AND ABOVE NET DRIFT (MORTALITY)

European Area	Country	Period curvature			Cohort curvature		
		Δ Deviance[1]	Δ d.f.[2]	*p*-value[3]	Δ Deviance[1]	Δ d.f.[2]	*p*-value[3]
Northern	Denmark	21.9	5	<0.01	34.6	12	<0.01
	Finland	18.5	5	<0.01	13.9	12	0.31
	Ireland	23.0	5	<0.01	11.6	12	0.48
	Norway	26.1	5	<0.01	21.5	12	0.04
	Sweden	35.2	5	<0.01	23.5	12	0.02
	United Kingdom	35.3	4	<0.01	81.3	11	<0.01
Eastern	Bulgaria	15.5	4	<0.01	15.3	11	0.17
	Czech Republic	0.4	1	0.55	19.1	8	0.01
	Hungary	18.0	4	<0.01	88.7	11	<0.01
	Poland	2.9	1	0.09	11.4	8	0.18
	Romania	8.8	2	0.01	12.9	9	0.17
Southern	Croatia	0.4	1	0.54	4.7	8	0.79
	Greece	1.3	4	0.86	21.5	11	0.03
	Italy	48.5	5	<0.01	17.9	12	0.12
	Portugal	1.2	2	0.56	18.9	9	0.03
	Spain	7.5	3	0.06	10.1	10	0.43
Western	Austria	44.4	5	<0.01	34.3	12	<0.01
	Belgium	5.6	4	0.23	5.7	11	0.89
	France	85.5	5	<0.01	32.2	12	<0.01
	Germany	1.3	1	0.25	48.6	8	<0.01
	The Netherlands	20.5	5	<0.01	28.4	12	<0.01
	Switzerland	40.2	4	<0.01	29.3	11	<0.01

[1]The difference in the deviance of the Age+Drift model and the model with the non-linear effects of Period or Cohort added.–[2]The difference in the degrees of freedom of the Age+Drift model and the model with the non-linear effects of Period or Cohort added.–[3]To determine the statistical significance of the non-linear effect, the change in deviance was compared with the chi-squared distribution on the change in degrees of freedom between the models.

models already provided a reasonable fit, respectively, possibly because of a lack of power to reject these simpler models.[46] Trends in Finland, Norway and Slovenia required the full APC model, indicative of some period curvature being in operation, in addition to the cohort effects. Birth cohort effects can be viewed as a consequence of the changing prevalence of the risk determinants of the disease in successive generations, and generational increases of testicular germ-cell tumors are in accordance with the known biology of the disease, with possibly a role for external environmental factors mediated through exposure of the developing male embryo.[47] The sharp rise in incidence observed around the onset of puberty implies a role of male sex hormones in the progression of germ-cell tumors.

A reduced incidence amongst a specific cohort born during the Second World War was observed in a number of countries, particularly in Denmark and Norway, as has been reported previously.[6,7,37,41,48] It has been hypothesized that an altered supply of provisions in Denmark[9,37] may have impacted on consumption of a variety of foodstuffs and other commodities during the German military occupation. Interestingly, the pattern was also seen around the same time in Sweden, as previously reported,[6] and in Italy, Slovenia, France and Switzerland. In Spain, a cohort with minimum risk was also identified, but at least a decade later, in the late-1950s. In the remaining countries (Finland, the U.K., Slovakia and the Czech Republic), no such break in the generational increases was evident. That the observation arises in many European countries in men born around the period of the Second World War suggests that modifications in lifestyle, possibly brought about by a war-related supply restriction at this time, were strong determinants of the disease, and that they acted very early in life, given the transitory nature of the phenomenon.[9,37] If a dietary factor is involved, this would probably concern an alteration in maternal diet affecting the offspring prenatally or postnatally. A recent study hypothesized that the mycotoxin Ochratoxin A, a contaminator of stored foods such as cereals and coffee, may be a causal factor.[49]

Despite the increases in incidence, decreasing mortality trends of between 3 and 6% per annum were observed throughout Northern and Western Europe, and in Italy, the Czech Republic and Hungary. The starting point and the rate of decrease in each country appears closely related to the dramatic improvements in the survival of young and middle-aged patients, following the introduction of cisplatin as a therapeutic agent for advanced germ-cell tumors.[22] Notable declines were first observed in Denmark, Norway and the U.K in the early 1970s, followed soon after by Sweden, Finland and France. Further developments of cisplatin-based regimens, improvements in tumor imaging and surgical interventions of residual disease, together with a multidisciplinary approach to cancer care, have all contributed to the continuation of the declining mortality trends in the 1970s and 1980s.[50] Thus, in spite of the generation-specific increases in incidence, the risk of death has been on the decrease in generations of men born after 1940 in higher resource countries.

In several Eastern Europe countries, where death rates are currently highest, the rate of decrease was of a relatively low order of magnitude, in part due to a later decline around the mid to late 1980s, at least a decade after Northern and Western Europe. The notable success of chemotherapy in terms of reductions in mortality were thus not uniformly seen across Europe, and slower and later declines in some lower resource countries imply that the high cost of appropriate treatments together with inadequate patient management systems are responsible for the high mortality rates and less favorable trends. Of particular and immediate concern were the increases in testicular cancer mortality in Portugal and Croatia of 2% and over 4% per annum, respectively. The trends were, in the majority of countries, based on small numbers, and particular interpretation was difficult at a more detailed level. The cohort analysis, however, clearly shows that the risk of death from testicular cancer has increased among men born in these countries since 1950.

Regarding our age-period-cohort analysis, the choice of slopes should be ideally founded on biological or epidemiological evidence; otherwise, if erroneous, a bias in all of the effects may be incurred.[51] Selecting a range of slopes leaves some margin for error, allowing the researcher to contrast the age, period and cohort effects, based on their particular preference(s) for the fixed slope, with other less plausible specifications.[51] Our approach to presenting trends estimates using the age-period-cohort model was predisposed *a priori* toward a cohort-based approach for

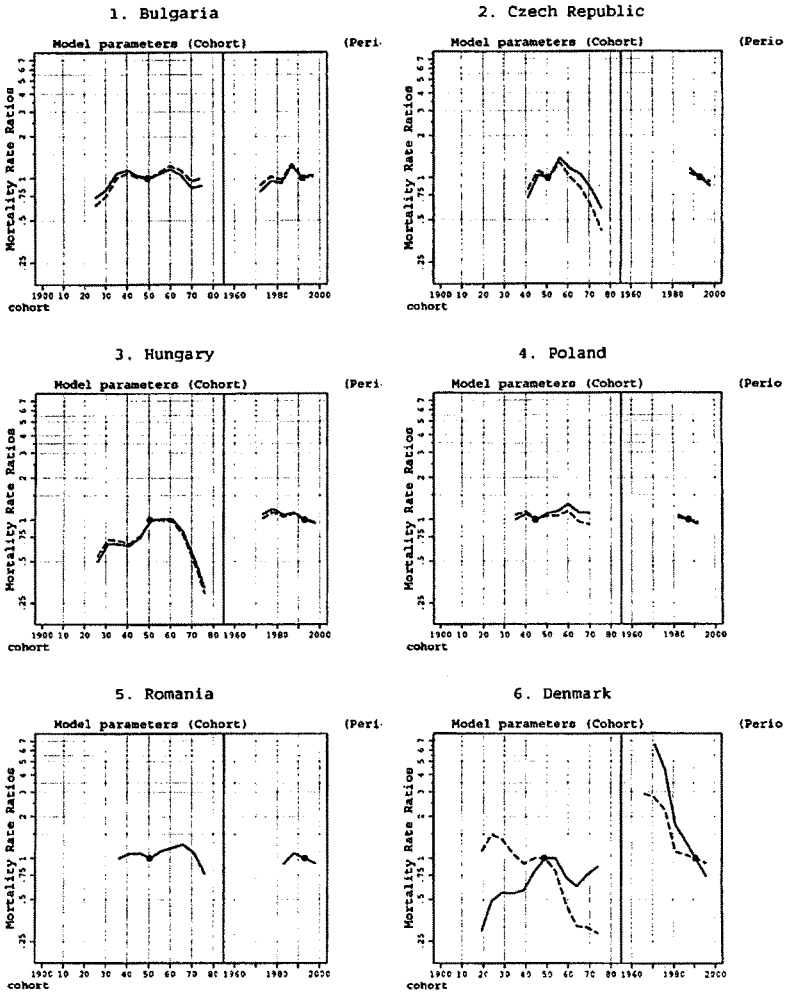

FIGURE 3 – Age period cohort parameters based on assumptions on period slope: mortality trends by country within European area (Panels 1–2: E Europe; 2–7: N Europe; 8–10: S Europe; 11–12: W Europe). Solid line: assumption of zero cohort slope (drift taken up entirely by period); dashed line: assumption of equal and same-direction slopes for period and cohort (drift attributed equally to period and cohort).

incidence, given that both epidemiological evidence and biological mechanisms point to the importance of generational influences on disease occurrence. We thus circumvented the nonidentifiability problem and presented unique estimates of the period and cohort effects by firstly assuming a period slope of zero, implying that birth cohort influences were entirely responsible for the time trend; secondly, acknowledging the possibility of some increases in rates across all age groups over a period of

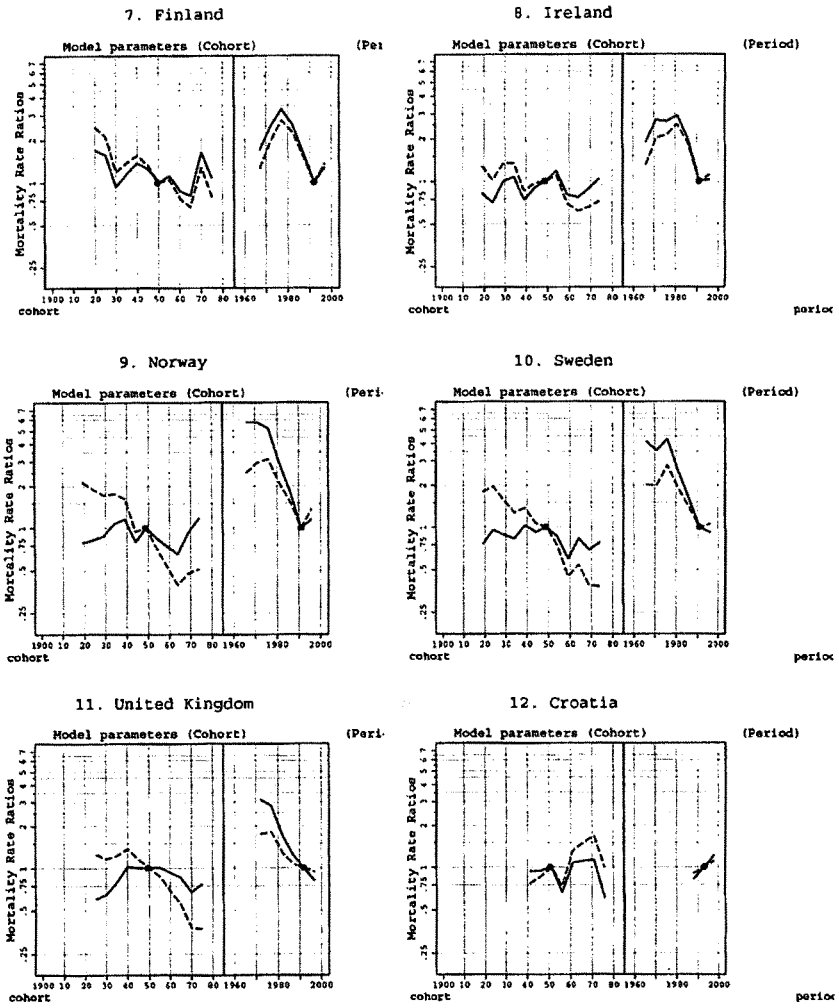

FIGURE 3 – CONTINUED.

time, the regular trend was attributed equally to period and cohort slopes.

For mortality, *a priori* evidence suggested that the presentation of the trends should incorporate the well-known benefits from treatment, which should show up as period-related effects. Mirroring the approach to incidence, we assumed firstly that the regular trend was a result of period influences, setting the cohort slope to zero. A second set of presented estimates accounted for the possi-

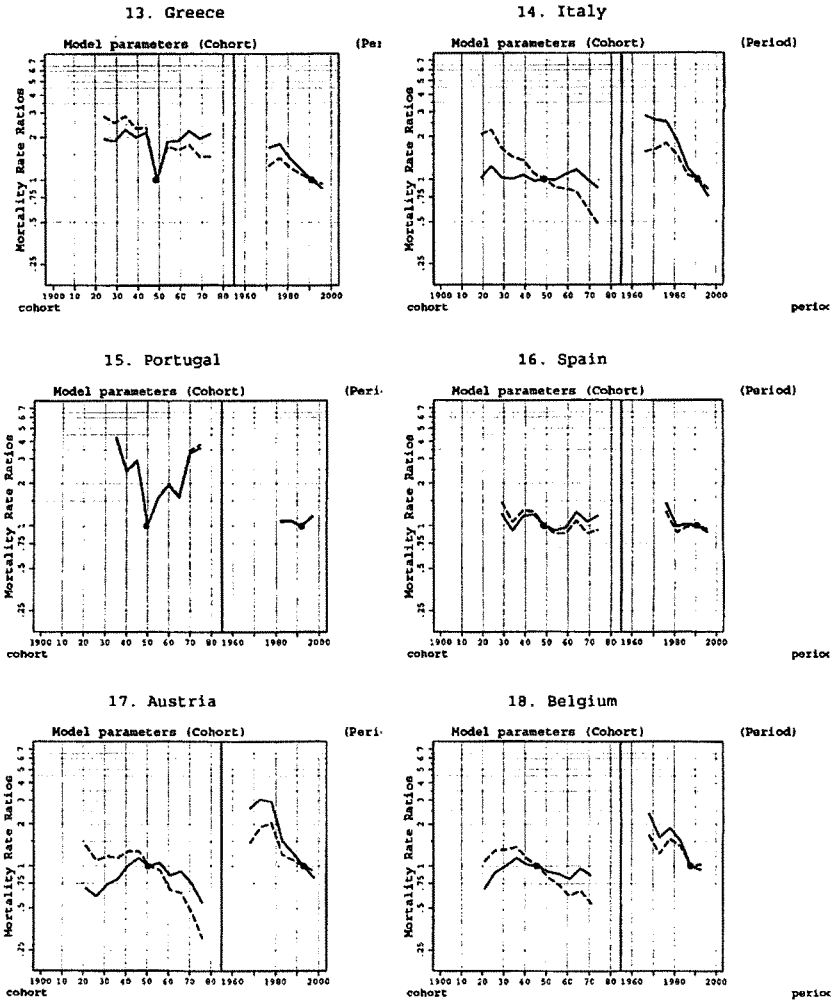

FIGURE 3 – CONTINUED.

bility of generational influences related to disease occurrence; the regular trend was then apportioned evenly to the slopes of period and cohort, as was for incidence.

The testicle is a visible and palpable organ, and so, the origin of the tumor is usually evident, notably among young and middle-aged men. Hence, misclassification and underascertainment of registration are less of an issue than for most other malignancies. Palpable availability of the testicle together with standardized therapeutic approaches and primary inguinal orchiectomy provides the basis for the high proportion of histologically verified tumors.

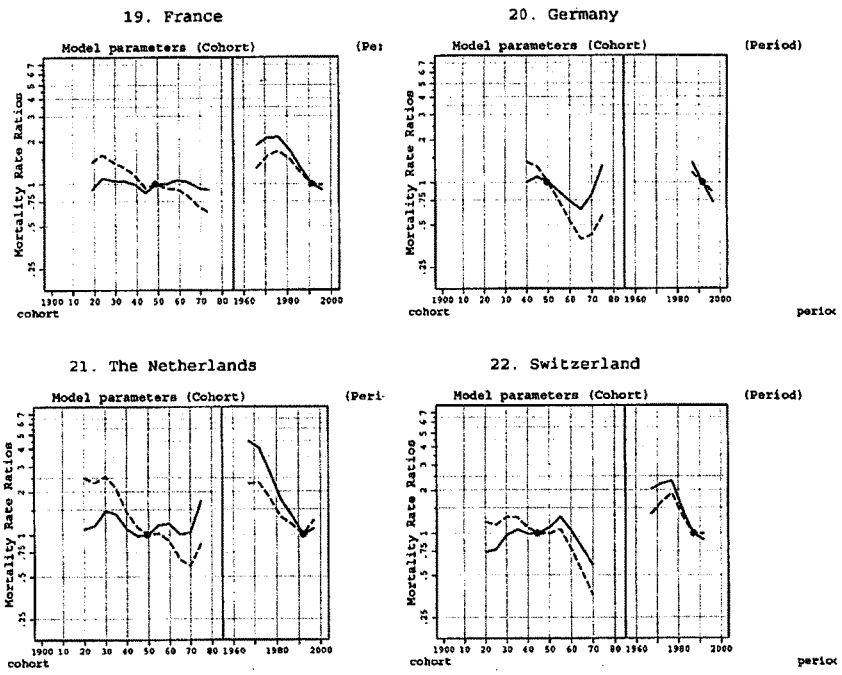

FIGURE 3 – CONTINUED.

This study provides a description of the current trends in testicular cancer incidence and mortality in Europe. Uniform increases in testicular germ-cell cancer varied 6-fold in 12 countries for which the background risk ranged 5-fold, with the importance of cohort effects clearly discernible. The underlying risk factors responsible for the increases remain elusive, though the extent of variation perhaps lends some support to the idea of an epidemic in different phases in different countries. Fortunately, advances in therapy and the management of testicular cancer since the mid 1970s have led to large declines in mortality in some European countries, despite the unabated increases in incidence. More disturbing, in lower-resource countries, has been the apparently slower progress toward delivery of optimal care reflected in the time trends of mortality. In countries like Bulgaria and Romania, the first beneficiaries of therapy appear to be men born—rather than diagnosed—in the era of this major breakthrough in oncology.

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References

1. Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB.Cancer incidence in five continents. vol.8. Lyon: IARC, 2002. Publication no. 155.
2. Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2000: cancer incidence, mortality and prevalence worldwide. IARC Cancer Base No. 5. Lyon: IARC, 2001.
3. Coleman MP, Estève J, Damiecki P, Arslan A, Renard H. Trends in cancer incidence and mortality, no. 121. Lyon: IARC, 1993.1–806.
4. Forman D, Moller H. Testicular cancer. Cancer Surv 1994;19/20: 323–41.
5. Adami HO, Bergstrom R, Mohner M, Zatonski W, Storm H, Ekbom A, Tretli S, Teppo L, Ziegler H, Rahu M, Gurevicius R, Stengrevics A. Testicular cancer in nine northern European countries. Int J Cancer 1994;59:33–8.
6. Bergstrom R, Adami HO, Mohner M, Zatonski W, Storm H, Ekbom A, Tretli S, Teppo L, Akre O, Hakulinen T. Increase in testicular cancer incidence in six European countries: a birth cohort phenomenon. J Natl Cancer Inst 1996;88:727–33.
7. Richiardi L, Bellocco R, Adami HO, Torrang A, Barlow L, Hakulinen T, Rahu M, Stengrevics A, Storm H, Tretli S, Kurtinaitis J, Tyczynski JE, et al. Testicular cancer incidence in eight northern European countries: secular and recent trends. Cancer Epidemiol Biomarkers Prev 2004;13:2157–66.
8. Moller H, Jorgensen N, Forman D. Trends in incidence of testicular cancer in boys and adolescent men. Int J Cancer 1995;61:761–4.
9. Moller H. Clues to the aetiology of testicular germ cell tumours from descriptive epidemiology. Eur Urol 1993;23:8–13.
10. Akre O, Ekbom A, Hsieh CC, Trichopoulos D, Adami HO. Testicular nonseminoma and seminoma in relation to perinatal characteristics. J Natl Cancer Inst 1996;88:883–9.
11. Coupland CA, Forman D, Chilvers CE, Davey G, Pike MC, Oliver RT. Maternal risk factors for testicular cancer: a population-based case-control study (UK). Cancer Causes Control 2004;15:277–83.
12. Moller H, Skakkebaek NE. Testicular cancer and cryptorchidism in relation to prenatal factors: case-control studies in Denmark. Cancer Causes Control 1997;8:904–12.
13. Wanderas EH, Grotmol T, Fossa SD, Tretli S. Maternal health and pre- and perinatal characteristics in the etiology of testicular cancer: a prospective population- and register-based study on Norwegian males born between 1967 and 1995. Cancer Causes Control 1998;9:475–86.
14. Sabroe S, Olsen J. Perinatal correlates of specific histological types of testicular cancer in patients below 35 years of age: a case-cohort study based on midwives' records in Denmark. Int J Cancer 1998;78:140–143.
15. Weir HK, Marrett LD, Kreiger N, Darlington GA, Sugar L. Pre-natal and peri-natal exposures and risk of testicular germ-cell cancer. Int J Cancer 2000;87:438–43.
16. English PB, Goldberg DE, Wolff C, Smith D. Parental and birth characteristics in relation to testicular cancer risk among males born between 1960 and 1995 in California (United States). Cancer Causes Control 2003;14:815–25.
17. Richiardi L, Akre O, Lambe M, Granath F, Montgomery SM, Ekbom A. Birth order, sibship size, and risk for germ-cell testicular cancer. Epidemiology 2004;15:323–9.
18. Moller H, Prener A, Skakkebaek NE. Testicular cancer, cryptorchidism, inguinal hernia, testicular atrophy, and genital malformations: case-control studies in Denmark. Cancer Causes Control 1996;7:264–74.
19. Sharpe RM, Skakkebaek NE. Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? Lancet 1993;341:1392–5.
20. Clemmesen J. Is pregnancy smoking causal to testis cancer in sons? A hypothesis. Acta Oncol 1997;36:59–63.
21. Pettersson A, Kaijser M, Richiardi L, Askling J, Ekbom A, Akre O. Women smoking and testicular cancer: one epidemic causing another?. Int J Cancer 2004;109:941–4.
22. Einhorn LH, Donohue J. Cis-diamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer. Ann Intern Med 1977;87:293–8.
23. Peckham MJ, McElwain TJ, Barrett A, Hendry WF. Combined management of malignant teratoma of the testis. Lancet 1979;2:267–70.
24. Sant M, Aareleid T, Berrino F, Bielska LM, Carli PM, Faivre J, Grosclaude P, Hedelin G, Matsuda T, Moller H, Moller T, Verdecchia A, et al. EUROCARE-3: survival of cancer patients diagnosed 1990-94-results and commentary. Ann Oncol 2003;14 (Suppl 5):V61–V118.
25. Levi F, la Vecchia C, Boyle P, Lucchini F, Negri E. Western and eastern European trends in testicular cancer mortality. Lancet 2001;357: 1853–4.
26. Kaye SB, Boyle P. The impact of chemotherapy in germ cell tumours. Cancer Surv 1989;8:631–46.
27. European Network of Cancer Registries. EUROCIM Version 4.0 2001.
28. Parkin DM, Muir CS, Whelan SL, Gao YT, Ferlay J, Powell J.Cancer incidence in five continents. vol.6. Lyon: IARC, 1992.
29. Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J.Cancer incidence in five continents. vol.7. Lyon: IARC, 1997.
30. McCullagh P, Nelder JA. Generalized linear models,2nd ed. London: Chapman and Hall, 1989.
31. StataCorp. Stata Statistical Software. Version 8.0. College Station, TX: StataCorp; 2003.
32. Clayton D, Schifflers E. Models for temporal variation in cancer rates. I. Age-period and age-cohort models. Stat Med 1987;6:449–67.
33. Clayton D, Schifflers E. Models for temporal variation in cancer rates. II. Age-period cohort models. Stat Med 1987;6:469–81.
34. Holford TR. The estimation of age, period and cohort effects for vital rates. Biometrics 1983;39:311–24.
35. Holford TR. Age-period-cohort analysis. Encyclopedia of biostatistics. Chichester: Wiley, 1998;82–99.
36. Davies JM. Testicular cancer in England and Wales: some epidemiological aspects. Lancet 1981;1:928–32.
37. Moller H. Decreased testicular cancer risk in men born in wartime. J Natl Cancer Inst 1989;81:1668–9.
38. Levi F, Te VC, la Vecchia C. Testicular cancer trends in the Canton of Vaud, Switzerland, 1974–1987. Br J Cancer 1990;62:871–3.
39. Grunet RF, MacMahon B. Trends in mortality from neoplasms of the testis. Cancer 1958;11:790–7.
40. Clemmesen J. A doubling of morbidity from testis carcinoma in Copenhagen, 1943–1962. Acta Pathol Microbiol Scand 1968;72:348–9.
41. Rajpert-De Meyts E, Bartkova J, Samson M, Hoei-Hansen CE, Frydelund-Larsen L, Bartek J, Skakkebaek NE. The emerging phenotype of the testicular carcinoma in situ germ cell. APMIS 2003;111:267–78.
42. Swerdlow AJ, Huttly SR, Smith PG. Testicular cancer and antecedent diseases. Br J Cancer 1987;55:97–103.
43. United Kingdom Testicular Cancer Study Group. Aetiology of testicular cancer: association with congenital abnormalities, age at puberty, infertility, and exercise. BMJ 1994;308:1393–9.
44. Richiardi L, Akre O, Montgomery SM, Lambe M, Kvist U, Ekbom A. Fecundity and twinning rates as measures of fertility before diagnosis of germ-cell testicular cancer. J Natl Cancer Inst 2004;96:145–7.
45. Akre O, Ekbom A, Sparen P, Tretli S. Body size and testicular cancer. J Natl Cancer Inst 2000;92:1093–6.
46. Kaldor JK, Day NE. Mathematical models in cancer epidemiology. In: Schottenfeld D, Fraumeni JF, Jr, eds. Cancer epidemiology and prevention, 2nd ed. New York: Oxford, 1996;127–37.
47. Moller H. Trends in incidence of testicular cancer and prostate cancer in Denmark. Hum Reprod 2001;16:1001–11.
48. Wanderas EH, Tretli S, Fossu SD. Trends in incidence of testicular cancer in Norway 1955–1992. Eur J Cancer 1995;31A:2044–8.
49. Schwartz GG. Hypothesis: does ochratoxin A cause testicular cancer? Cancer Causes Control 2002;13:91–100.
50. Power DA, Brown RS, Brock CS, Payne HA, Majeed A, Babb P. Trends in testicular carcinoma in England and Wales, 1971–99. BJU Int 2001;87:361–5.
51. Holford TR. Understanding the effects of age, period, and cohort on incidence and mortality rates. Ann Rev Public Health 1991;12:425–57.

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