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TRUTH REVEALED: NEW SCIENTIFIC DISCOVERIES REGARDING MERCURY IN MEDICINE AND AUTISM

HEARING

BEFORE THE

SUBCOMMITTEE ON HUMAN RIGHTS AND WELLNESS

OF THE

COMMITTEE ON GOVERNMENT REFORM

HOUSE OF REPRESENTATIVES

ONE HUNDRED EIGHTH CONGRESS

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TRUTH REVEALED: NEW SCIENTIFIC DISCOVERIES REGARDING MERCURY IN MEDICINE AND AUTISM

WEDNESDAY, SEPTEMBER 8, 2004

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HUMAN RIGHTS AND WELLNESS,
COMMITTEE ON GOVERNMENT REFORM,
Washington, DC.

The committee met, pursuant to notice, at 10 a.m., in room 2154, Rayburn House Office Building, Hon. Dan Burton, (chairman of the committee) presiding.

Present: Representatives Burton, Watson, Murphy, and Cummings.

Staff present: Danielle Perraut, clerk; Mark Walker, staff director; Mindi Walker, Dan Getz, and Brian Fauls, professional staff members; Nick Mutton, press secretary; Sarah Despres, minority counsel; and Cecelia Morton, minority office manager.

Mr. BURTON. A quorum being present, the Subcommittee on Human Rights and Wellness will come to order.

I ask unanimous consent that all Members' and witnesses' written and opening statements be included in the record. Without objection, so ordered.

I ask unanimous consent that all articles, exhibits and extraneous or tabular materials referred to be included in the record. Without objection, so ordered.

In the event of other Members attending the hearing, I ask unanimous consent that they be permitted to serve as a member of the subcommittee for today's hearing, and without objection, so ordered.

We have with us from the 18th District of Pennsylvania Representative Tim Murphy. Representative Murphy is very interested in this issue and we really appreciate him being here.

Representative Watson will be here in just a few minutes.

The subcommittee is convening today to discuss the latest scientific research regarding the use of mercury in medicine in the United States and the possible connection between these products and autism spectrum disorders. The subcommittee will also discuss the need for further research to determine the biological basis of autism and how the Federal Government is working to decrease the occurrences of this health epidemic in the United States.

During my tenure as the chairman of the full Committee on Government Reform and as the current chairman of this subcommittee, I have convened no fewer than 20 hearings on the topics of autism,

vaccine safety and the detrimental health effects of mercury-containing medical products. During these investigations, numerous scientists from all around the world have testified before this committee and the full committee. They have presented credible, peer-reviewed research studies that indicated a direct link between the exposure of mercury, a widely known neurotoxin, and the increasing incidence of autism.

Just recently we found that, I think the EPA was complaining about the excessive amount of mercury in our waterways in and around the central United States, the Great Lakes and so forth, and how that's having an adverse impact on neurological disorders across this country. It continues to mystify me how we can say that it has to be taken out of the environment and yet we continue to inject it into our children and into adults and expect there not to be some kind of adverse reaction.

Mercury has been present in medicines dispersed widely to the public for decades. Unknown to most Americans, mercury is still present in medicines that we use every day, including eye drops, nasal spray, as well as many anti-fungal and anti-itch creams, as well as vaccines. While the pharmaceutical industry has found new ways to manufacture many medicines and vaccinations that don't require the use of mercury, three vaccines that currently remain on the mandatory pediatric vaccine schedule still contain the mercury derivative thimerosal, and those vaccines are the DTAP, which is called the diphtheria, tetanus and pertussis vaccine, the flu vaccine and hepatitis B.

We've been complaining about mercury in children's vaccines now for about 4 or 5 years. And it's been removed from most children's vaccines except those three.

My grandson, as I've said before, got nine shots in 1 day, seven of which had mercury in them. Just a few days later, he became autistic. This is a story that we've heard from many parents who have testified before this committee over the years. And yet, we continue to see mercury used as a preservative.

Now, although it's been taken out of a lot of the children's vaccines, the shelf life on many of those vaccines is pretty long. Mercury-containing vaccines are still on the shelf, even though they're not being produced. So in addition to these three vaccines that are still being produced using mercury, there are others that are on the shelf right now that doctors are still using that children are being vaccinated with. And I think it's a crying shame.

Although I applaud the benefits that many vaccines have provided Americans over the years, I am perplexed as to why we are administering shots containing poisonous toxins to our children, when technology has ceased the need for this otherwise harmful preservative. The debate over whether or not there are linkages between mercury and neurodevelopmental diseases has become more heated in recent times.

Six years ago, when I started an investigation into the detrimental health effects of mercury, the science supporting these claims was sparse. Recently, credible researchers from many of our Nation's most highly regarded research universities have published studies noting the possible associations between mercury and health defects.

Dr. Richard Deth, professor at the College of Pharmaceutical Studies at Northeastern University, was the lead researcher in a collaboration between Johns Hopkins University, Tufts University, the University of Nebraska and Northeastern University on a groundbreaking study into the possible correlation between increases in environmental toxins, such as thimerosal, and the incidence of autism. Dr. Deth will testify on the findings and future implications of his research.

Another innovative study was conducted at Columbia University recently, released in June of this year. The researchers exposed mice to thimerosal in doses and timing which corresponds to the current pediatric immunization schedule. The independent Columbia University study indicates that subjects with a specific genetic susceptibility toward autism are placed at a greater risk for neurodevelopmental diseases when administered thimerosal-containing vaccine.

Unfortunately, Dr. Mady Hornig, the lead researcher on this project, is unable to be with us this morning due to a personal emergency. But in her place, Dr. Deth will present her oral testimony.

In a partnership between the University of Pittsburgh, Carnegie Mellon University and the University of Illinois, funded by the National Institute of Child Health and Development, participating scientists have begun looking at the neural science of autism on a wide scale, multi-million dollar project.

A brain scanning technique identified as FMRI, or functional magnetic resonance imaging, was used in this experiment to compare the brain activity of adults afflicted with high functioning autism with non-autistic participants. The researchers then specifically examined two regions of the brain associated with language skills. To better explain the findings of this study, the subcommittee has the pleasure of receiving testimony from Dr. Marcel Just, one of the lead researchers on this monumental study.

To discuss the implications of using mercury in medical devices, the subcommittee will be hearing testimony from my good friend, Dr. Richard Fischer, a practicing dentist and representative of the International Academy of Oral Medicine and Toxicology.

As many of us already know, the incidence of autism have become increasingly prevalent in modern day society. Once considered a rare disease, affecting roughly 1 in 10,000 children, autism now affects 1.5 million of our Nation's children. And this problem continues to escalate rapidly.

According to a recent Autism Alarm released by the U.S. Department of Health and Human Services, the Centers for Disease Control and the American Academy of Pediatrics, currently one out of every six children is diagnosed with a developmental disorder and/or behavioral problem. Even more alarming, 1 out of every 166 children in the United States is being diagnosed with an autism spectrum disorder. From 1 in 10,000 to 1 in 166. This major health care crisis has clearly reached epidemic proportions and will not simply go away.

To address the current CDC observations with regard to the autism epidemic, the subcommittee will be receiving testimony from Dr. Melinda Wharton, Medical Doctor, the Acting Deputy Director

of the National Immunization Program at CDC, who will be speaking about information her office has collected regarding the incidence and prevalence of autism in the United States.

The FDA's Center for Biologics Evaluation and Research is responsible for the regulation and oversight of vaccines administered here in the United States. Dr. William Egan, Acting Director of the Office of Vaccine Research and Review at CBER will be testifying today on how the FDA has worked to reduce the exposure of thimerosal to children in the United States. I will be very interested in hearing that.

To give a perspective into the challenges facing the families of autistic individuals, Lyn Redwood, a registered nurse and mother of an autistic child, will be informing the subcommittee on these issues. In addition to her professional and personal obligations, Ms. Redwood is also the president and founder of the Coalition for SafeMinds, Sensible Action for Ending Mercury-Induced Neurological Disorders, an organization founded to investigate and raise awareness about the autism spectrum disorders.

While the science behind the causation of autism is being deliberated, I firmly believe that we should take every precaution to ensure the health and well-being of every American. By eliminating mercury from medicine, we are taking a vital first step. Even if there was not a lot of evidence, and I believe conclusive evidence, that mercury in vaccines and in other areas is causing neurological disorders, it seems to me even if there is the most remote possibility, we would get it out of there.

I mean, every time I talk to people who appear before the committee, either privately or in public forum, I say to them, would you mind if we just took the thimerosal, the mercury, and injected it into you like they did our kids? And they will say to you, well, I don't think I want mercury injected into our bodies. And these are doctors who say there's no harm being done. But they don't want mercury stuck in their bodies with a needle.

Yet we do it to our kids every single day, and we do it to adults. And we wonder why there's an increase in the rates of autism, these epidemic increases, 1 out of 166. And we wonder why we see more and more people coming down with Alzheimer's disease. And we find out that mercury is in the environment and they're saying we've got to get it out of the environment because of the problems with the neurology of our population. Yet we continue to put it into our bodies with needles. I just don't understand it.

But in any event, I look forward to hearing the testimony from our witnesses. With that, Ms. Watson, it's nice to see you. As usual, you look very fashionable today.

[The prepared statement of Hon. Dan Burton follows:]

Opening Statement of Chairman Dan Burton
Government Reform Committee
Subcommittee on Human Rights & Wellness
"Truth Revealed: New Scientific Discoveries Regarding Mercury in Medicine and Autism"
September 8, 2004

The Subcommittee is convening today to discuss the latest scientific research regarding the use of Mercury in medicine in the United States and the possible connection between these products and Autism Spectrum Disorders. The Subcommittee will also discuss the need for further research to determine the biological basis of autism, and how the Federal Government is working to decrease the occurrences of this health epidemic in the United States.

During my tenure as the Chairman of the Full Committee on Government Reform, and as the current Chair of this Subcommittee, I have convened no fewer than 20 hearings on the topics of Autism, vaccine safety, and the detrimental health effects of Mercury-containing medical products.

During these investigations, numerous scientists from around the globe have testified before the Committee, and have presented credible peer-reviewed research studies that indicated a direct link between the exposure of Mercury, a widely known neurotoxin, and the increasing incidences of autism.

Mercury has been present in medicines dispersed widely to the public for decades. Unbeknownst to most Americans, Mercury is still present in medicines we use everyday, including: eye drops, nasal spray, as well as many antifungal and anti-itch creams.

While the pharmaceutical industry has found new ways to manufacture many medicines and vaccinations that don't require the use Mercury, three (3) vaccines that currently remain on the MANDATORY pediatric vaccine schedule still contain the Mercury-derived preservative Thimerosal: DTaP (Diphtheria, Tetanus, and Pertusis), Flu, and Hepatitis B.

Although I applaud the benefits that many vaccines have provided Americans over the years, I am perplexed as to why we are administering shots containing poisonous toxins to our children when technology has ceased the need for this otherwise harmful preservative.

The debate over whether or not there are linkages between Mercury and neurodevelopmental diseases has become more heated in recent times. Six years ago, when I started an investigation into the detrimental health effects of Mercury, the science supporting these claims was sparse.

Recently, credible researchers from many of our Nation's most highly regarded research universities have published studies noting the possible associations between Mercury and health defects.

Dr. Richard Deth (Deeth), Professor at the College of Pharmaceutical Studies at Northeastern University, was the lead researcher in a collaboration between Johns Hopkins University, Tufts University, the University of Nebraska, and Northeastern University on a groundbreaking study into the possible correlation between increases in environmental toxins such as thimerosal and incidences of autism. Dr. Deth will testify on the findings and future implications of his research.

Another innovative study was conducted at Columbia University recently. Released in June of this year, the researchers exposed mice to Thimerosal in doses and timing, which corresponds to the current pediatric immunization schedule.

The independent Columbia University study indicates that subjects with a specific genetic susceptibility toward autism are placed at a greater risk for neurodevelopmental diseases when administered Thimerosal-containing vaccines. Unfortunately, Dr. Mady Hornig (May-dee, Horn-ig), the lead researcher on this project, is unable to be with us this morning due to a personal emergency. In her place, Dr. Deth (Deeth) will present her oral testimony.

In a partnership between the University of Pittsburgh, Carnegie Mellon University, and the University of Illinois - funded by the National Institute of Child Health and Development - participating scientists have begun looking at the neural science of autism on a wide-scale multi-million dollar project.

A brain-scanning technique identified as "fMRI", or functional magnetic-resonance imaging, was used in this experiment to compare the brain activity of adults afflicted with high-functioning autism with non-autistic participants. The researchers then specifically examined two regions of the brain associated with language skills. To better explain the findings of this study, the Subcommittee has the pleasure of receiving testimony from Dr. Marcel Just, one of the lead researchers on this monumental study.

To discuss the implications of using Mercury in medical devices, the Subcommittee will be hearing testimony from my good friend, Dr. Richard Fischer, a practicing dentist and representative of the International Academy of Oral Medicine and Toxicology (IAOMT).

As many of us already know, the incidences of autism have become increasingly prevalent in modern-day society. Once considered a rare disease, effecting roughly 1 in 10,000 children, autism now affects 1.5 Million of our Nation's children, and this problem continues to escalate rapidly.

According to a recent "Autism Alarm" released by the U.S. Department of Health and Human Services (HHS), the Centers for Disease Control (CDC), and the American Academy of Pediatrics, currently 1 out of every 6 children are diagnosed with a developmental disorder and / or behavioral problem.

Even more alarming, today 1 out of every 166 children in the United States is being diagnosed with an Autism Spectrum Disorder. This major healthcare crisis is clearly reaching epidemic proportions, and will not just simply "go away."

To address the current CDC observations with regard to the autism epidemic, the Subcommittee will be receiving testimony from Dr. Melinda Wharton, M.D. the Acting Deputy Director of the National Immunization Program at CDC, who will be speaking about information her office has collected regarding the incidence and prevalence of autism in the United States.

The FDA's Center for Biologics Evaluation and Research (CBER) is responsible for the regulation and oversight of vaccines administered in the United States. Dr. William Egan, Acting Director of the Office of Vaccines Research and Review at CBER will be testifying today on how the FDA has worked to reduce the exposure of thimerosal to children in the United States.

To give a perspective into the challenges facing the families of autistic individuals, Lyn Redwood, a Registered Nurse and mother of an autistic child will be informing the Subcommittee on these issues. In addition to her professional and personal obligations, Ms. Redwood is also the President and Founder of the Coalition for Safeminds (Sensible Action For Ending Mercury-Induced Neurological Disorders), an organization founded to investigate and raise awareness about the Autism Spectrum Disorders.

While the science behind the causation of autism is being deliberated, I firmly believe that we should take every precaution to ensure the health and well

being of every American. By eliminating Mercury from medicine, we are taking a vital first step. As Hippocrates (Hip-paw-crat-tease), the father of Medicine, stated in *Regimen of Health*, " A wise man should consider that health is the greatest of human blessings and learn how by his own thought to derive benefit from his illnesses."

I would like to thank all of our witnesses for being with us today to speak on this most important matter, and I look forward to hearing their testimony.

News From...

The Subcommittee on Human Rights and Wellness

Chairman Dan Burton (R ~ IN)

http://www.house.gov/reform

For Immediate Release:
September 7, 2004

Contact: Nick Mutton
(202) 225-2276

CHAIRMAN BURTON TO EXAMINE NEW SCIENCE CONNECTING MERCURY AND AUTISM

Washington, D.C. – Congressman Dan Burton (R-IN), Chairman of the House Government Reform Subcommittee on Human Rights & Wellness, will convene a hearing to examine the latest scientific research out of leading universities such as Columbia, Johns Hopkins, Northeastern, and Carnegie Mellon, regarding the harmful effects of mercury in the human body. The Subcommittee will also discuss the need for additional research to determine the biological basis for autism, as well as how specifically the U.S. Centers for Disease Control (CDC) are reviewing the occurrences of this health epidemic.

The Subcommittee's oversight hearing, entitled ***"Truth Revealed: New Scientific Discoveries Regarding Mercury in Medicine and Autism," will be held on Wednesday, September 8, 2004, in Room 2154 of the Rayburn House Office Building at 10:00 a.m.***

Stated Chairman Burton, "I strongly believe the information presented in these recent credible scientific studies from our nation's most highly regarded research universities, will shed important new light on the debate over a link between vaccines and autism. It should be crystal clear to both our health officials and the general public by now that mercury is a toxic substance that does not belong in pediatric vaccines. There is simply no need to take the risk."

In May 2004, the Institutes of Medicine (IOM) released its eighth, and final report examining the hypothesis that thimerosal-containing vaccines are causally associated with autism. The IOM concluded there was no such association between thimerosal-containing vaccines and autism - a marked departure from their 2001 report, which called a causal relationship "biologically plausible" - and recommended that no further research to evaluate this issue be funded. However, shortly thereafter in June 2004, the Mailman School of Public Health at Columbia University published findings from their independent study of several strains of mice – those with a certain genetic susceptibility and those without – that were exposed to thimerosal in doses and timing, which corresponds to the current pediatric immunization schedule. The research indicated that the subjects with a specific genetic susceptibility led to responses and activities that mimic those found in Autism Spectrum Disorders (including growth retardation, social withdraw, gross motor coordination, and hyperactivity).

Several distinguished researchers from the various participating universities will be on hand to further explain their groundbreaking studies and discuss the impact of their findings on future research of autism and other neurodevelopmental disorders.

PANEL ONE WITNESS:

Representative *(Invited)*
Centers for Disease Prevention (CDC)
United States Department of Health & Human Services

PANEL TWO WITNESSES:

Dr. Richard Deth
Bouve College of Health Sciences
Department of Pharmaceutical Services
Northeastern University

Dr. Marcel Just
D.O. Hebb Professor of Psychology
Director, Center for Cognitive Brain Imaging
Carnegie Mellon University

Dr. Mady Hornig
Assistant Professor of Epidemiology
Columbia University

Dr. Richard Fischer, D.D.S.
International Academy of Oral Medicine & Toxicology

Ms. Lyn Redwood
President, Safeminds

Chairman Burton has held more than twenty hearings on the topics of autism, vaccine safety, and the detrimental effects of mercury-containing medical products. For more information, or to access hearing resource materials, please visit the Subcommittee's website at www.reform.house.gov/WHR.

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Ms. WATSON. I want to thank our chairman very much for pursuing this particular topic. I join him as a committed ally.

So over the last several years, our chairman has investigated potential health problems associated with the use of mercury in medicine, including the use of a mercury-containing preservative in vaccines called thimerosal and the use of mercury in dental amalgams. These are issues that I have been involved with for a long time. I understand the paramount importance of having vaccines and dental amalgams and dental materials that work. Vaccines save thousands of lives every year, and poor oral health is a major cause of suffering in this country. But the question is, whether we can achieve these goals without using mercury, a known neurotoxin.

Now, let me start with dental amalgam, an issue that has been of major concern to me for years. Over the last century and a half, mercury-containing amalgam has been the most widely used dental device in the United States. Yet important studies about the safety of amalgam, including some underway at the National Institutes of Health, have not been completed? Why?

In 1992, I authored a bill that passed the California Legislature, requiring disclosure of the risks and efficacies of various types of dental materials. In the past month, the California dental board is finally, is finally disseminating a fact sheet to inform the public about these materials. This is an important step forward, and I commend them. But more needs to be done for the law to be fully implemented.

Chairman Burton and I have corresponded with the Food and Drug Administration on the subject of dental amalgam. We are trying to determine why the FDA has failed to put dental amalgam into a particular class of medical devices. I am pleased FDA is represented at this hearing today, and I would hope that the representatives would address this issue.

I am also interested in hearing about progress in research on dental amalgam, including studies that were discussed at previous meetings this committee has held. In addition to hearing from FDA, I look forward to Dr. Richard Fischer's testimony on the regulatory status of dental amalgam.

Now, let me turn to the issue of vaccine. Since our last meeting, the Institute of Medicine released a major report investigating a potential link between thimerosal in vaccines and autism. The Institute of Medicine reviewed published and unpublished studies and concluded that available evidence favors rejection of the theory that thimerosal in vaccine causes autism. Some scientists and parents have expressed concern about this report, and today we will hear from several scientists who have conducted recent research on thimerosal and autism.

Some of this research was considered by the Institute of Medicine but did not figure prominently in its report. The testimony today should be very enlightening and interesting. A timely concern relates to the use of mercury in flu vaccines. Flu kills tens of thousands of Americans every year, and protecting infants, children and adults from this deadly virus is essential. At the same time, I think we all can agree that it would be ideal for the flu vaccine to be mercury-free.

So I'm interested in hearing from those who will be presenters today. And I want to know why, particularly from our CDC, why our Nation's leading public health authority has not endorsed this idea.

And on a personal note, Mr. Chairman, I have been pursuing the amalgam issue for over a decade. So I decided that I would get the amalgam in my fillings that I have had since I was 9 years old removed. I had to go to Mexico to do it. My own dentist didn't have a clue, and argued with me that it was safe.

But as I gather information and I chaired the California Health and Human Services Committee for 17 out of the 20 years I was in the California State Senate, and I had an expert staff that dug up the information and the research, enough that I knew that my health would improve if I had it removed. I had it removed, and my health improved immediately. Went back over the border to the United States, had dental work, and I have a temporary covering that has amalgam in it, and I can see the difference in my complexion and my look. I was being poisoned, Mr. Chairman, all of those years, by the amalgam vapors that were escaping because the tooth next to it was pulled, and it leaves exposure.

So I don't buy the argument the professional dental community came to my office to give me in opposing my bill. And they said, it's cheap, it's sealed and it will not hurt. Well, kids chew hard balls, and dentures, dental teeth crack and the vapors escape, and they go up to the meninges of the brain, causing considerable damage. So I myself am a victim and I'm going to pursue this issue until we can come to some agreement about the best policy.

So thank you for coming, and I look forward to hearing from you. Thank you, Mr. Chairman.

Mr. BURTON. Thank you, Ms. Watson.

Representative Murphy.

Mr. MURPHY. Thank you, Mr. Chairman. As you know, I am not a member of this subcommittee, although I am a member of the full committee, and I appreciate the opportunity to sit on this subcommittee with you. Rather than take time now, I would like to go on and listen to the witnesses today. Thank you, sir.

Mr. BURTON. Very good, thank you.

Our first panel consists of William Egan, Ph.D., Acting Director of the Office of Vaccines, Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration, Department of Health and Human Services, and Melinda Wharton, M.D., MPH, Acting Deputy Director of the National Immunization Program, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. I presume you have somebody there with you that you'd like to introduce. Who else do we have there? Dr. Egan, Dr. Wharton and Dr. Boyle?

Dr. WHARTON. Yes, Dr. Coleen Boyle, from CDC.

Mr. BURTON. OK. Will she be testifying as well?

Dr. WHARTON. She is available to answer questions should there be questions that fall into her area of expertise.

Mr. BURTON. OK. Would you please rise to be sworn?

[Witnesses sworn.]

Mr. BURTON. Thank you.

Dr. Wharton, would you like to start?

STATEMENT OF MELINDA WHARTON, M.D., M.P.H., ACTING DEPUTY DIRECTOR, NATIONAL IMMUNIZATION PROGRAM, CENTERS FOR DISEASE CONTROL AND PREVENTION, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, ACCOMPANIED BY COLEEN BOYLE, ASSOCIATE DIRECTOR FOR SCIENCE AND PUBLIC HEALTH

Dr. WHARTON. Good morning. I'm Dr. Melinda Wharton, Acting Deputy Director of the National Immunization Program at the Centers for Disease Control and Prevention. Thank you for the opportunity to testify today on CDC's vaccine safety research activities, particularly those regarding thimerosal-containing vaccines.

I am accompanied today by Dr. Colleen Boyle, Associate Director for Science and Public Health with CDC's National Center for Birth Defects and Developmental Disabilities, who is here to help answer questions on CDC's autism related activities.

CDC understands that autism can be a devastating illness and impacts families and caregivers alike. CDC joins with other Federal and State agencies and other partners in their continued search to learn more about the causes. Autism spectrum disorders are a group of lifelong developmental disabilities caused by an abnormality of the brain. The most recent data suggests that between two and six children per thousand have autism spectrum disorders. However, one of CDC's goals is to obtain better information on the incidence and prevalence of these disorders.

The emotional, social and economic impact on families and children diagnosed with autism spectrum disorders is often devastating, and the cost to the Nation in human and economic terms is substantial and needs to be better documented. The Department of Health and Human Services is dedicated to finding the answers to what causes autism and how it can be prevented.

There's a great deal of ongoing research throughout the various public health agencies. But my focus today is on the vaccine safety related issues. It should be noted that the Department of Health and Human Services has established an inter-agency action coordinating committee [IACC], composed of representatives to various Federal agencies as well as four members of the public. The IACC's mandate is to enhance coordination of autism-related activities of these Federal agencies from biomedical research to service delivery.

Immunizations are one of the great public health success stories of the 20th century, having made once common diseases like diphtheria, measles and mumps diseases of the past. Vaccines are now available to protect children and adults against 15 life-threatening or debilitating diseases. This has reduced cases of all vaccine-preventable diseases for which children are now routinely vaccinated by more than 97 percent, from peak levels before the vaccines were available, saving lives and treatment and hospitalization costs.

However, we know that parents, researchers and others have expressed concerns about a potential link between autism and vaccines containing thimerosal, a preservative used to reduce the possibility of bacterial or fungal contamination of vaccine. Other than minor effects, like swelling and redness at the injectionsite due to sensitivity to thimerosal, there is no definitive evidence of harm caused by the amounts of thimerosal in vaccine.

After an FDA analysis of the potential mercury content of the full recommended childhood vaccination schedule and concern about health effects of mercury exposures from all sources in mid-1999, the U.S. public health service agencies took precautionary action, working collaboratively with the American Academy of Pediatrics and the vaccine manufacturers to begin the voluntary removal of thimerosal preservative from the vaccine supply.

While the risk of harm from exposure to thimerosal in vaccines is only theoretical, the decision was made as a precautionary measure. The elimination of mercury from vaccines was judged a feasible means of reducing an infant's total exposure to mercury in a world where other environmental sources of exposure are more difficult or impossible to eliminate.

As a result of this action, all manufacturers are now producing only vaccines that are free of thimerosal as a preservative for routine infant immunization, with the exception of influenza vaccines. As of January 14, 2003, the final lots of the routinely recommended infant vaccines that contained thimerosal as a preservative, with the exception of influenza vaccine, expired.

CDC is actively involved in detecting and investigating vaccine safety concerns and in supporting a wide range of vaccine safety research to address safety questions. CDC developed the vaccine safety data link project in 1990 to better enhance the understanding of rare adverse effects of vaccines. This project was a collaborative effort utilizing the data bases of large health maintenance organizations. The data bank contains comprehensive medical and immunization histories of approximately 7.5 million children and adults. The VSD enables vaccine safety research studies comparing the incidence of health problems in unvaccinated and vaccinated people.

CDC recognizes the importance of data sharing when questions are raised regarding a particular study's designer methodology. Therefore, CDC has worked with the participating HMOs to determine how their clients' personal medical records can be maintained confidentially while still allowing for external researchers to reanalyze the data from studies which have been conducted through the VSD. As a result, CDC has developed a data sharing process operated by the National Center for Health Statistics designed to allow independent researchers to replicate or conduct a modified analysis of a previous VSD study while maintaining the confidential nature of the data.

Another critical part of our vaccine safety effort is the objective scientific evaluation of safety concerns by independent experts. In collaboration with NIH and other public health service agencies, CDC requested the Institute of Medicine, one of the world's preeminent medical organizations, to conduct independent reviews by objective, highly qualified scientific experts to determine whether the available scientific information tends to show or does not tend to show vaccines played a role in causation, the level of public health priority that concern should receive and recommendations for research.

As you have already noted, in May 2004, the IOM Immunization Safety Review Committee updated its previous report regarding vaccines and autism based on the additional studies that have been

done on the topic since its 2001 report. The IOM concluded that thimerosal-containing vaccines are not associated with autism, that hypotheses regarding the links between autism and thimerosal-containing vaccines lacked supporting evidence and were only theoretical, and that future research to find the cause of autism should be directed toward other promising lines of inquiry that are supported by current knowledge and evidence and offer more promise for providing the answer.

CDC takes the issue of vaccine safety very seriously and has initiated several studies that address IOM recommendations in its previous report. The first study, the thimerosal screening analysis in the VSD was started in the fall of 1999. The VSD was used to screen for possible associations between exposure to thimerosal-containing vaccines and a variety of outcomes. In a first phase of this study, the CDC used data from the two VSD HMOs with automated outpatient data. An association between cumulative exposure to thimerosal and tics was found in one HMO. At the other HMO, slightly increased risks of language delay were found, but there was no increased risk of tics.

In the second phase of the investigation, CDC investigators obtained data from a third HMO with similar, available automated vaccination in outpatient data bases to see if these findings could be replicated. Analyses of these data using the same methods as the first study did not confirm results seen in the first phase.

To determine if these associations are real or by chance, the usual scientific approach is to conduct other studies to confirm or not confirm the initial results. No statistically significant relationship between autism and thimerosal was found in any of CDC's analyses of the FSD data. The findings of the study were published in Pediatrics in November.

CDC and VSD researchers remain committed to clarifying the results encountered during the VSD screening analysis, and therefore a followup study is being conducted. This study will be designed to assess whether neurodevelopmental disorders confirmed by uniform neuropsychologic testing are associated with thimerosal exposure.

Approximately 1,100 children between the ages of 7 and 9 randomly selected from the 4 VSD HMOs, based on thimerosal exposure during the first 7 months of life, are being evaluated. All of the children will be assessed using a standard set of neuropsychological test batteries. Data collection is nearing completion and the testing has been completed and medical records are now being reviewed. Preliminary study results should be available in the spring of 2005.

The vaccine safety data link and autism study is a case control study that will begin data collection this fall. Autism cases identified through the review of automated medical records from three VSD HMOs will be assessed using a standard autism assessment tool. CDC is also funding a followup study of a group of Italian children who participated in a prior DTAP trial in the 1990's in which thimerosal exposure was randomly allocated. The children will be evaluated similarly as we're doing in the followup study. Testing of the children will begin in the fall.

Though we remain vigilant to assure the safety of vaccines, we also must remember that vaccines benefit the public by protecting persons from infectious diseases and the consequences. Continued high vaccination rates are crucial to prevent the spread of diseases such as measles, pertussis and rubella among U.S. children. From 1989 to 1991, a measles epidemic in the United States led to more than 55,000 cases of measles and more than 11,000 hospitalizations and 123 deaths. The outbreak stopped only when vaccination coverage increased.

Thus, if preschool vaccine coverage drops substantially, large measles outbreaks are likely to occur once again. The threats posed by vaccine preventable diseases are known and real. The viruses and bacteria that cause vaccine preventable diseases still circulate in the United States and around the world. Maintaining vaccination coverage and high levels of immunity are crucial to protect the U.S. population and to continue progress toward elimination of diseases that at one time caused millions of infections in the United States each year and globally remain the leading causes of death.

CDC remains committed to collecting accurate data on the prevalence of autism, conducting public health research on autism and conducting studies on vaccine safety. Vaccines are one of our most valuable weapons against disease and have afforded to us one of our proudest achievements in public health. Autism research and monitoring will continue to be high priorities for CDC. Such efforts will be essential in answering key questions about whether autism is increasing over time, determining the causes of this condition and ultimately developing prevention strategies.

In addition to these critical efforts, we also realize the need to act on existing science to improve the lives of children already living with this condition by providing developmental screening and intervention. We want each child to be born healthy and to grow and develop to their full potential.

Thank you, Mr. Chairman and members of the committee, for the opportunity to testify before you today. Dr. Boyle and I will be happy to answer any questions that you may have.

[The prepared statement of Dr. Wharton follows:]

Testimony
Before the Subcommittee on Human Rights and Wellness
Committee on Government Reform
United States House of Representatives

CDC's Vaccine Safety Research Activities

Statement of

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Good morning. I am Dr. Melinda Wharton, Acting Deputy Director of the National Immunization Program at the Centers for Disease Control and Prevention (CDC). Thank you for the opportunity to testify today on CDC's vaccine safety research activities, particularly those regarding thimerosal-containing vaccines and autism. I want to take a moment to introduce Dr. Coleen Boyle, Associate Director for Science and Public Health with CDC's National Center for Birth Defects and Developmental Disabilities who is also available to help answer questions on CDC's autism-related activities.

CDC understands that autism can be a devastating illness that impacts families and caregivers alike. CDC joins with other federal and state agencies, and other partners in the continued search to learn more about the causes.

AUTISM AND VACCINES

Autism spectrum disorders (ASD) are a group of life-long developmental disabilities caused by an abnormality of the brain. The most recent data suggests that between two and six children per 1,000 have ASD; however, one of CDC's goals is to obtain better information on the incidence and prevalence of ASDs. The emotional, social and economic impact on families of children diagnosed ASDs is often devastating and the costs to the nation in human and economic terms is substantial but needs to be better documented. We recognize that there is considerable public interest and concern on this issue and we are committed to addressing concerns of parents, families, caregivers and health care providers. The Department of Health and Human Services (DHHS) is dedicated to finding the answer to what causes autism and how it can be prevented. There is a great deal of ongoing research throughout the various public health agencies. While my focus today is on vaccine safety related issues, it should be noted that DHHS has established an Interagency Autism Coordinating Committee (IACC). The IACC is composed of representatives from the National Institutes of Health (to which the Department has delegated a leadership role in organizing and supporting the committee), CDC (including the Agency for Toxic Substances and Disease Registry (ATSDR)), the Food and Drug Administration, the Health Resources and Services Administration (HRSA) the Substance Abuse and Mental Health Services Administration (SAMHSA),

the Department of Education, and four public members appointed by Secretary Tommy Thompson. The IACC's mandate is to enhance coordination of the autism-related activities of these federal agencies, from biomedical research to services delivery. At the most recent IACC meeting, topics included the progress being made on implementation of autism research centers programs by NIH and CDC; efforts to comprehensively map the autism research field to analyze its strengths and any gaps; information about each of the individual grants that collectively constitute the majority of the NIH autism research portfolio; strategies to improve the coordination of gene and tissue banking, data sharing, and federal interactions with voluntary organizations; and, strategic planning for the development of treatments and interventions for autism. The activities of this committee highlight the large-scale, coordinated response that has been launched by DHHS to better understand, prevent and treat autism.

CDC also is holding four regional meetings to obtain more public input into the CDC portion of the IACC agenda; these meetings are being held over the next four months in Miami, FL; Sacramento, CA; Indianapolis, IN and in New York City.

Immunizations are one of the great public health success stories of the 20th century, having made once-common diseases, such as diphtheria, measles, mumps, and pertussis, diseases of the past. Vaccines are now available to protect children and adults against 15 life-threatening or debilitating diseases. This has reduced cases of all vaccine-preventable diseases by more than 97 percent from peak levels before vaccines were available, saving lives and saving treatment and hospitalization costs. However, some parents, researchers and others have expressed concerns about a potential link between autism and vaccines containing thimerosal, a preservative used to reduce the possibility of bacterial or fungal contamination of vaccines. Other than minor effects like swelling and redness at the injection site due to sensitivity to thimerosal, there is no definitive evidence of harm caused by the amounts of thimerosal in vaccines.

After an FDA analysis of the potential mercury content of the full recommended childhood vaccination services and concern about the health effects of mercury exposures

from all sources in mid-1999, the United States Public Health Service agencies, including NIH, FDA, HRSA, and CDC took precautionary action, working collaboratively with the American Academy of Pediatrics, the American Academy of Family Physicians and the vaccine manufacturers, to begin the voluntary removal of thimerosal preservative from the vaccine supply. While the risk of harm from exposure to thimerosal in vaccines was only theoretical, the decision was made as a precautionary measure. The elimination of mercury from vaccines was judged a feasible means of reducing an infant's total exposure to mercury in a world where other environmental sources of exposure are more difficult or impossible to eliminate, such as removal from certain foods and power emissions. As a result of this action, all manufacturers are now producing only vaccines that are free of thimerosal as a preservative for routine infant immunization, with the exception of influenza vaccine. As of January 14, 2003, the final lots of the routinely recommended childhood vaccines that contained thimerosal as a preservative, with the exception of influenza vaccine, expired.

CDC'S COMMITMENT TO VACCINE SAFETY

CDC is actively involved in detecting and investigating vaccine safety concerns and supporting a wide range of vaccine safety research to address safety questions.

Vaccine Safety Datalink Project

CDC developed the Vaccine Safety Datalink (VSD) project in 1990 to better enhance the understanding of rare adverse effects of vaccines. This project is a collaborative effort, which utilizes the databases of eight large health maintenance organizations (HMOs). The database contains comprehensive medical and immunization histories of approximately 7.5 million children and adults. The VSD enables vaccine safety research studies comparing incidence of health problems between unvaccinated and vaccinated people. Over the past decade, the VSD has been used to answer many vaccine-related questions, and has been used to support policy changes that have reduced adverse effects from vaccines.

CDC recognizes the importance of data sharing when questions are raised regarding a particular study's design and methodology. Therefore, CDC worked with the participating HMOs to determine how their clients' personal medical records can be maintained confidentially and the proprietary interests of the HMOs protected, while still allowing for external researchers to reanalyze the data from studies which have been conducted through the Vaccine Safety Datalink. As a result, CDC has developed a data sharing process operated by the National Center for Health Statistics in collaboration with the National Immunization Program, which is designed to allow independent researchers to replicate or conduct a modified analysis of a previous VSD study, while maintaining the confidential and proprietary nature of the data.

Institute of Medicine Immunization Safety Review Committee

Another critical part of our vaccine safety efforts is the objective, scientific evaluation of safety concerns by independent experts. In collaboration with NIH and other U.S. Public Health Service agencies, CDC requested the Institute of Medicine (IOM), one of the world's predominant medical organizations, to conduct independent reviews by objective, highly qualified scientific experts to determine: 1) whether the available scientific information tends to show, or does not tend to show, vaccines playing a role in causation; 2) the level of public health priority the concern should receive; and, 3) recommendations for research. The IOM Immunization Safety Review Committee has released reports on STET, Multiple Immunizations and Immune Dysfunction, and most recently Vaccines and Autism CDC has initiated a broad range of studies to address recommendations made by the IOM Immunization Safety Review Committee.

In October 2001, the IOM Immunization Safety Review Committee published a report on the possible association between thimerosal-containing vaccines and neurodevelopmental disorders. In this report, the IOM concluded "that the evidence is inadequate to accept or reject a causal relationship between exposure to thimerosal from childhood vaccines and the neurodevelopmental disorders of autism, ADHD (attention deficit hyperactivity disorder), and speech or language delay." The IOM made several recommendations regarding future research studies including several epidemiological studies. They recommended:

- Case-control studies examining the potential link between neurodevelopmental disorders and thimerosal-containing vaccines;
- Further analysis of neurodevelopmental outcomes in several cohorts of children outside the U.S. who participated in a clinical trial of DTaP vaccine; and,
- Conducting epidemiological studies that compare the incidence and prevalence of neurodevelopmental disorders before and after the removal of thimerosal from vaccines.

In May 2004, the IOM Immunization Safety Review Committee updated its conclusions and recommendations regarding vaccines and autism based on the additional studies that had been done on this topic since 2001. The IOM Immunization Safety Review Committee's most notable conclusions regarding thimerosal-containing vaccines were:

- thimerosal-containing vaccines are not associated with autism;
- hypotheses regarding a link between autism and thimerosal-containing vaccines lack supporting evidence and are only theoretical; and,
- future research to find the cause of autism should be directed toward other promising lines of inquiry that are supported by current knowledge and evidence and offer more promise for providing an answer.

The Committee also made a number of recommendations in the areas of policy, surveillance, and epidemiologic research, clinical studies, and communication in regard to thimerosal-containing vaccines, including:

- the Committee did not recommend a policy review of the current schedule and recommendations for the administration of routine childhood vaccines based on hypotheses regarding thimerosal and autism;
- the Committee recommended that cost-benefit assessments regarding the use of thimerosal-containing versus thimerosal-free vaccines and other biological or pharmaceutical products, whether in the United States or other countries, should not include autism as a potential risk; and,

- the Committee recommended developing programs to increase public participation in vaccine safety research and policy decisions and to enhance the skills and willingness of scientists and government officials to engage in constructive dialogue with the public about research findings and their implications for policy development.

The Committee has made helpful recommendations about policy and research in the areas of vaccine safety and autism. These will be considered in depth by the Public Health Service (PHS) agencies and their advisory bodies. At this time, CDC is making no changes to the current childhood immunization schedule and recommendations based on hypotheses regarding vaccines and autism.

Vaccine Safety Studies

CDC takes the issue of vaccine safety very seriously and therefore undertook several studies that addressed the IOM recommendations from the 2001 report:

The first study, the Thimerosal Screening Analysis in the Vaccine Safety Datalink (VSD) project, was started in the fall of 1999. The VSD, described earlier, was used to screen for possible associations between exposure to thimerosal-containing vaccines and a variety of renal, neurologic and developmental problems. In the first phase of this study, the CDC used data from the 2 VSD HMOs with automated outpatient data (where more subtle effects of mercury toxicity might be seen). In phase I, an association between cumulative exposure to thimerosal and tics was found at one HMO. At the other HMO, slightly increased risks of language delay were found but there was no increased risk of tics. In the second phase of the investigation, CDC investigators examined data from a third HMO with similar available automated vaccination and outpatient databases to see if these findings could be replicated. Analyses of these data using the same methods as the first study did not confirm results seen in the first phase. I should note for the committee that it is not uncommon to find associations between health outcomes and an exposure of interest when multiple different health outcomes are assessed. To determine if those associations are real or occur by change, the usual scientific approach is to

conduct other studies to confirm or not confirm the initial results. I also want to note that a statistically significant relationship between autism and thimerosal was not found in any of CDC's analysis of the VSD data. The findings from this study were published in the journal *Pediatrics* in November 2003.

CDC and VSD researchers remain committed to clarifying the results encountered during the VSD Screening Analysis; therefore, a Thimerosal and Neurodevelopmental Disorders (NDD) Follow-Up Study is being conducted. This second study will be designed to assess whether preliminary results from automated data used in the Thimerosal Screening Analysis can be confirmed using objective neuropsychological testing. The study will focus on the conditions found in the first screening analyses and other important neurodevelopmental disorders, including language and speech delays and ADHD. The design of the new study will address the main drawback of the Thimerosal Screening Analysis, which was that children were not objectively assessed on the neurodevelopmental disorders of interest. The various VSD HMOs categorize neurodevelopmental disabilities in different ways, provide different services for these disorders, and often refer children out of the health care network when they are identified with these particular disorders.

The Thimerosal and NDD Follow-Up Study will examine approximately 1,100 children between the ages of seven and nine years of age randomly selected from four VSD HMOs based on thimerosal exposure during the first seven months of life. All 1,100 children will be assessed using a standardized set of neuropsychological test batteries. The proposal for this study was presented to a panel of external consultants including a consumer representative in March of 2001. The panel of external consultants continues to provide individual input into the design and the conduct of the study. Data collection is nearing completion. The neuropsychological testing of the children has been completed and currently their medical records are being reviewed. The preliminary study results should be available for review by the external consultants by the spring of 2005.

Several additional studies are being planned to address additional issues raised by the IOM. These include:

The Vaccine Safety Datalink Thimerosal and Autism Study is a case-control study that will begin data collection this fall and will complement the Thimerosal and NDD Follow-Up Study. Autism cases identified through review of automated medical records from three VSD HMOs will be assessed objectively by using standardized autism assessment tools. Three controls per case will be selected from the same HMOs.

CDC is also funding a follow-up study of a group of Italian children who had participated in a prior DTaP trial in the 1990's in which thimerosal exposure was randomly allocated. A pilot study has determined the feasibility of recruiting these participants for a follow-up study of neurodevelopmental outcomes. The children will be evaluated using a similar test battery as in the Thimerosal and NDD Follow-Up Study. Testing of children for the main study will begin this fall.

Two other studies are being planned to examine changes over time in the diagnosis of neurodevelopmental delays including autism. These studies use inpatient and outpatient discharge diagnoses to compare rates of these conditions over time with changes in levels of thimerosal in recommended childhood vaccines. Because recommendations for the removal of thimerosal from vaccines did not occur until 1999, several years of data following the removal of thimerosal are necessary for these comparisons to be made. Thus, results will not be available until 2006 or later.

BENEFITS OF VACCINES

While we remain vigilant to assure the safety of vaccines, we must also remember that vaccines benefit the public by protecting persons from infectious diseases and their consequences e.g. liver cancer. Continued high U.S. vaccination rates are crucial to prevent the spread of diseases such as measles, pertussis (whooping cough) and rubella among U.S. children. Current measles coverage is approximately 91 percent in children 19-35 months old and about 97 percent at school entry, and only about 100 cases of

measles have been reported per year; many of the cases are imported; and ongoing indigenous transmission of measles no longer occurs. From 1989-91, a measles epidemic in the United States led to more than 55,000 cases of measles and more than 11,000 hospitalizations, with 123 deaths in three years. Before this epidemic, vaccination coverage was estimated at 61-66 percent nationally and at 51-79 percent in 15 major cities. These outbreaks stopped only when vaccination coverage increased. Thus, if pre-school coverage dropped by 25-30 percent below the current level, large measles outbreaks are likely to occur once again. Additionally, pertussis has continued to be a public health threat. For example, in 2003, there were 11,647 reported pertussis cases with 19 reported deaths.

Vaccines are cited as one of the greatest achievements of biomedical science and public health in the 20th century. We can point to the remarkable success we have had in controlling numerous infectious diseases which used to be widely prevalent in the United States, including polio, measles, and pertussis. In fact, several of these vaccine-preventable infectious diseases are associated with developmental disabilities, including Haemophilus influenzae type b (Hib) and congenital rubella syndrome (CRS). Prior to routine immunization with Hib vaccine, of young children who developed Hib meningitis, 5 percent died and another 15 to 30 percent were left with residual brain damage leading to language disorders and mental retardation.

The threats posed by vaccine-preventable diseases are known and real. The viruses and bacteria that cause vaccine-preventable diseases still circulate in the U.S. and around the world. Maintaining vaccination coverage and high levels of immunity are crucial to protect the U.S. population and to continue progress toward elimination of diseases that, at one time, caused millions of infections in the U.S. each year and that globally remain the leading causes of death.

CONCLUSION

CDC remains committed to collecting accurate data on the prevalence of autism, conducting public health research on autism, and conducting studies on vaccine safety. Vaccines are one of our most valuable weapons against disease and have afforded us one of our proudest achievements in public health. Autism research and monitoring will continue to be high priorities for CDC. Such efforts will be essential in answering key questions about whether autism is increasing over time, determining the cause(s) of this condition, and ultimately developing prevention strategies. In addition to these critical efforts, we also realize the need to act on existing science to improve the lives of children already living with this condition by promoting developmental screening and intervention. We want each child to be born healthy and to grow and develop to their full potential.

Thank you, Mr. Chairman and Members of the Committee, for the opportunity to testify before you today. Dr. Boyle and I would be happy to answer any questions that you may have.

Mr. BURTON. Thank you for your testimony. Everybody knows the value of vaccinations. And every time you testify, you tell us how valuable they've been. And we already know that.

We're not here to say that vaccinations aren't important. They're very important. They've given us the highest quality of life of any civilization in the history of mankind. That isn't what we're talking about. We're talking about why they're putting mercury in vaccinations and why it's never been tested since 1929 when Lily developed it.

Mr. Egan.

STATEMENT OF WILLIAM EGAN, PH.D., ACTING DIRECTOR, OFFICE OF VACCINES RESEARCH AND REVIEW, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. EGAN. Mr. Chairman and members of the committee, I am Dr. William Egan, the Acting Director for the Office of Vaccines Research and Review of the Food and Drug Administration Centers for Biologics Research and Review.

FDA's Office of Vaccine Research and Review is responsible for the regulation and oversight of vaccines in the United States. On behalf of the FDA, I appreciate the opportunity to participate in this hearing as the committee explores the hypothesized link between thimerosal in vaccines and autism. I want to assure the committee, the public and the parents who are here today that FDA takes this issue and their concerns very seriously.

As you know, vaccines have contributed to a significant reduction in many childhood diseases, such as diphtheria, polio, measles and whooping cough. It is now rare for American children to experience the devastating effects of these illnesses, and infant deaths due to these diseases have essentially disappeared in countries with high vaccination coverage, such as the United States.

As a recent example, prior to the introduction of a vaccine in 1985, an estimated 20,000 cases of invasive hemophilus influenza type A disease, primarily meningitis, occurred each year in the United States. Now because of widespread vaccination, the number of cases of invasive HIB disease have decreased by more than 98 percent. In the United States, HIB disease had been the leading cause of acquired mental retardation.

Although vaccines have contributed greatly to the health and well-being of our children, we must nonetheless be vigilant for any potential safety concerns that are related to these vaccines. In response to Section 413 of the Food and Drug Administration Modernization Act of 1997, FDA conducted a review of, among other things, the use of thimerosal in childhood vaccines. This review led to the realization that some children, during the first 6 months of life, may receive amounts of ethylmercury from the preservative thimerosal in excess of EPA guidelines for methylmercury, while though not the guidelines for either the ATSDR or the FDA.

Although there were no known risks from these levels of thimerosal in vaccines, the Public Health Service, along with the American Academy of Pediatrics and the American Academy of Family Physicians, thought that it was prudent to reduce childhood expo-

sure to mercury from all sources, including vaccines, whenever possible. Consistent with this goal, FDA has encouraged and worked with manufacturers to develop new vaccines and new vaccine formulations that are either thimerosal-free or contain only trace amounts of thimerosal.

We are pleased to report that FDA actions have resulted in a marked reduction in thimerosal exposure from vaccines. At this time, with the exception of the influenza vaccine, and I will address this vaccine in a moment, all of the routinely recommended pediatric vaccines, DTAP, hepatitis B, the pneumococcal conjugate vaccine, IPV, the HIB conjugate vaccine, MMR and varicella that are currently manufactured for the U.S. market are either thimerosal-free or contain only trace amounts of residual thimerosal.

As just noted, the exception is the inactivated influenza virus vaccine that has only recently been recommended for routine use in a pediatric population 6 months through 23 months of age. FDA has approved two preservative-free formulations of the inactivated influenza vaccine containing only a trace of mercury from thimerosal. One of these formulations is approved for use in the pediatric population. The other is not, it's for children above the age of 4. The two licensed manufacturers of the injectable form of the vaccine also do market this product in a thimerosal preservative-containing formulation.

The reduction or elimination of thimerosal was in principle achievable because over time, it has been possible to replace multidose vials with single dose vials which do not require a preservative. Prior to this initiative to reduce or eliminate thimerosal from childhood vaccines, the maximum cumulative exposure to mercury as ethylmercury via the routine pediatric vaccinations during the first 6 months of life was approximately 187.5 micrograms. The vaccines with trace amounts of thimerosal licensed to date contain less than 1 microgram of mercury per dose.

With the newly formulated vaccine, the maximum cumulative exposure during the first 6 months of life is less than 3 micrograms of mercury. This use of vaccines with no thimerosal or only trace amounts of thimerosal represents a greater than 98 percent reduction from previous maximum exposure to young infants. A table listing vaccines, preservative contents and the manufacturers can be found on FDA's Web site.

Although not administered to children below the age of 6 months, the influenza vaccine could add an additional 25 micrograms of mercury during the first year of life if each of the two doses that were administered both contain thimerosal as a preservative. Since the FDA last appeared before the committee to discuss this issue, we have approved several vaccines, new vaccines that are either thimerosal-free or contain only a trace amount of thimerosal.

These are Pediarix, which is a combination diphtheria, tetanus, toxoid and acellular pertussis vaccine with hepatitis B and inactivated polio vaccine. And this is manufactured by GlaxoSmithKline. Decovax, a tetanus and diphtheria toxoid absorbed vaccine, for adult use, mainly for ages 7 and up, manufactured by Aventis Pasteur Inc. A diphtheria and tetanus toxoids DP vaccine for pediatric use, this is also manufactured by Aventis Pasteur Inc. And a tetanus and diphtheria absorbed TB vaccine for

adult use manufactured by Aventis Pasteur Ltd. In addition, a live attenuated influenza virus vaccine that is thimerosal-free, Flu Mist, that was manufactured by Metamune, was licensed in 2003.

The Immunization Safety Committee of the Institute of Medicine has completed two reviews of studies addressing a potential link between thimerosal-containing vaccines and autism that are relevant to this hearing today. The first IOM review was conducted in 2001. In 2001, based on the data then available, the IOM concluded that the body of data was inadequate to either accept or reject a causal relationship between thimerosal-containing vaccines and neurodevelopmental disorders, including autism.

The committee, prompted by an accumulation of new data, re-reviewed this issue of the potential causal relation between thimerosal-containing vaccines and autism in 2004. Based on a review of the full body of data, which included epidemiological studies from the United States, Denmark, Sweden and the United Kingdom, the committee concluded, "Thus, based on this body of evidence, the committee concludes that the evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism."

The FDA has succeeded in reducing children's exposure to mercury from vaccines during the first 6 months of life. It continues toward reducing everyone's thimerosal exposure through vaccines. With the exception of the inactivated influenza vaccine, which just this year was added to the list of routinely recommended pediatric vaccines, all routinely recommended licensed pediatric vaccines that are currently being manufactured in the United States now contain no thimerosal or only trace amounts of thimerosal. FDA, together with our colleagues within the other HHS agencies, will continue to study data relating to the incidence and etiology of autism.

I would be happy to respond to any questions from the committee.

[The prepared statement of Dr. Egan follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

STATEMENT BY

WILLIAM EGAN, Ph.D.,
ACTING DIRECTOR

OFFICE OF VACCINES RESEARCH AND REVIEW

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON HUMAN RIGHTS AND WELLNESS

COMMITTEE ON GOVERNMENT REFORM

UNITED STATES HOUSE OF REPRESENTATIVES

SEPTEMBER 8, 2004

RELEASE ONLY UPON DELIVERY

Introduction

Mr. Chairman and Members of the Committee, I am Dr. William Egan, Acting Director, Office of Vaccines Research and Review (OVRR), of the Food and Drug Administration's (FDA or the Agency) Center for Biologics Evaluation and Research (CBER). CBER's Office of Vaccines Research and Review is responsible for the regulation and oversight of vaccines in the United States. On behalf of FDA, I appreciate the opportunity to participate in this hearing as the Committee explores the hypothesized link between thimerosal in vaccines and autism. I want to assure the Committee, the public and, the parents who are here today, that FDA takes their concerns very seriously. I will take this opportunity to explain FDA's ongoing efforts to ensure that vaccines in the U.S. are safe and effective.

As you know, vaccines have contributed to a significant reduction in many childhood diseases such as diphtheria, polio, measles, and whooping cough. It is now rare for American children to experience the devastating effects of these illnesses and infant deaths due to these diseases have essentially disappeared in countries with high vaccination coverage, such as the U.S. As a recent example, prior to the introduction of a vaccine in 1985, an estimated 20,000 cases of invasive *Haemophilus influenzae* type b (Hib) disease, primarily meningitis, occurred each year in the U.S. Now, because of widespread vaccination, the number of cases of invasive Hib disease has decreased by more than 98 percent; in the U.S., Hib disease was the leading cause of acquired mental retardation. Although vaccines have contributed greatly to the

health and well being of our children, we must nonetheless be vigilant of any potential safety concern related to vaccines.

Thimerosal Reduction in Vaccines

In response to Section 413 of the Food and Drug Administration Modernization Act (FDAMA) of 1997, FDA conducted a review of, inter alia, the use of thimerosal in childhood vaccines. This review led to the realization that some children, during their first 6 months of life, might receive amounts of ethylmercury, from the preservative, thimerosal, in excess of the Environmental Protection Agency's guidelines for methylmercury, although not the Agency for Toxic Substances and Disease Registry or FDA guidelines. Although there were no known risks from these levels of thimerosal in vaccines, the Public Health Service, along with the American Academy of Pediatrics and the American Academy of Family Physicians felt that it was prudent to reduce childhood exposure to mercury from all sources, including vaccines, as feasible.

Consistent with this goal, FDA has encouraged and worked with manufacturers to develop new vaccines and new vaccine formulations that are either thimerosal-free or contain only trace amounts of thimerosal as a preservative.

We are pleased to report that FDA actions have resulted in a marked reduction in thimerosal exposure from vaccines. At this time, with the exception of the influenza vaccine – and I will address this vaccine in a moment, all of the routinely recommended licensed pediatric

vaccines (DTaP, Hepatitis B, pneumococcal conjugate, IPV, MMR, and varicella) that are currently manufactured for the U.S. market are either thimerosal-free or contain only trace amounts of thimerosal. As just noted, the exception is the inactivated influenza virus vaccine that has only recently been recommended for routine use in a pediatric population, 6 months through 23 months of age. FDA approved two preservative-free formulations of the injectable influenza vaccine containing only a trace of mercury from thimerosal. One of these formulations is approved for use in the pediatric population. The two licensed manufacturers of the injectable influenzae vaccine also market their product in a thimerosal preservative-containing formulation.

The reduction or elimination of thimerosal was, in principle, achievable because over time it was possible to replace multi-dose vials with single dose vials, which do not require a preservative.

Prior to this initiative to reduce or eliminate thimerosal from childhood vaccines, the maximum cumulative exposure to mercury as ethylmercury via routine childhood vaccinations during the first 6 months of life was approximately 187.5 micrograms. The vaccines with trace amount of thimerosal licensed to date contain less than 1 microgram of mercury per dose. With the newly formulated vaccines, the maximum cumulative exposure during the first 6 months of life is less than three micrograms of mercury. This use of vaccines with no or only trace amounts of thimerosal represents a greater than 98 percent reduction from previous maximum exposure in young infants. A table listing vaccines,

preservative contents and manufactures and can be found on FDA's website: *www.fda.gov/cber/vaccine/thimerosal.htm.* Although not administered to children below the age of 6 months, the influenza vaccine could add an additional 25 micrograms of mercury during the first year of life, if each of the two doses contains thimerosal as a preservative. Since FDA last appeared before the Committee to discuss this issue, we have approved the following vaccines that are either thimerosal-free or contain only a trace amount of thimerosal:

- Pediarix: Diphtheria & Tetanus Toxoids & Acellurlar Pertussis Vaccine Adsorbed, Hepatitis B and Inactivated Poliovirus Vaccine Combined manufactured by GlaxoSmithKline Biologics.
- DECAVAC: Tetanus and Diphtheria Toxoids Adsorbed (Td), for adult use manufactured by Aventis Pasteur, Inc.
- Diphtheria and Tetanus Toxoids Adsorbed (DT), for pediatric use, manufactured by Aventis Pasteur, Inc.
- Tetanus and Diphtheria Toxoids Adsorbed (Td) for adult use, manufactured by Aventis Pasteur Ltd.

In addition, a live-attenuated influenza vaccine that is thimerosal free, FluMist, manufactured by MedImmune, was licensed in 2003 for those 5-49 years of age.

Institute of Medicine (IOM) Review

The Immunization Safety Review Committee of the Institute of Medicine (IOM) completed two reviews of studies addressing a potential link between thimerosal containing vaccines and

autism that are relevant to this hearing today. The first IOM review was conducted in 2001. In 2001, based on the data then available, the IOM concluded that the body of data was inadequate to either accept or reject a causal relationship between thimerosal-containing vaccines and neurodevelopmental disorders, including autism. The Committee, prompted by the accumulation of considerable new data, re-reviewed this issue of a potential causal relationship between thimerosal-containing vaccines and autism in 2004. Based on a review of this full body of data, which included epidemiological studies from the United States, Denmark, Sweden, and the United Kingdom, the Committee concluded: "Thus, based on this body of evidence, the committee concludes that the evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism."

Conclusion

FDA has succeeded in reducing children's exposure to mercury from vaccines during the first 6 months of life and continues to work toward reducing everyone's thimerosal exposure through vaccines. With the exception of the inactivated influenza vaccine, which just this year was added to the list of routinely recommended pediatric vaccines, all routinely recommended licensed pediatric vaccines that are currently being manufactured for the U.S. market contain no thimerosal or only trace amounts of thimerosal. FDA, together with our colleagues within the other Health and Human Service agencies, will continue to study data relating to the incidence and etiology of autism.

I would be happy to respond to any questions.

Mr. BURTON. Thank you, Dr. Egan.

You quoted the IOM study. I understand there were 14 or 15 studies that were included in that research that they did. One was from Denmark. The government of Denmark, as I understand it, administers these vaccines over there. And if they admitted that there was a problem with the mercury in the vaccines, the government could be held liable, is that not correct?

Mr. EGAN. I don't know what the liability issue is.

Mr. BURTON. Well, in any event, they have a vested interest in it. There were five studies that were pretty much discounted by reputable groups that said that there was a causal relationship between the mercury in vaccines and autism that were discounted by the IOM. It has been the opinion of not only myself but other Members that the pharmaceutical industry has a great deal of influence on a lot of these decisions.

And as a result, we continue to see reports come out saying, oh, there's no relationship between the mercury in vaccines and autism. And yet we've gone from 1 in 10,000 children that are autistic to, according to CDC, 1 in 166. Is that not correct, Dr. Wharton?

Dr. WHARTON. Yes, in our written testimony, it's 2 to 6 per 1,000 in our recent study in Atlanta.

Mr. BURTON. Two to six per thousand, yes.

Dr. WHARTON. Yes.

Mr. BURTON. Well, it was 1 in 10,000 before. And according to what we got from CDC, it's 1 in 166 now.

Dr. WHARTON. That's for all autism spectrum disorders, for autism, a report that was published last year was 3 per 1,000.

Mr. BURTON. Would you find the difference between the 1 in 166 and the 2 in 1,000?

Dr. WHARTON. Find the difference?

Mr. BURTON. Yes, what's the difference?

Dr. WHARTON. The one includes a much narrower definition of autism. The other one includes pervasive developmental disorders and other issues, such as Asperger's syndrome.

Mr. BURTON. Sounds like to me you're mincing words. The fact is, more and more kids are being damaged and becoming autistic, is that not correct?

Dr. WHARTON. The rate of autism does appear to be higher than it was, as you mentioned earlier.

Mr. BURTON. Is mercury considered a toxic substance?

Mr. EGAN. Yes.

Mr. BURTON. It is?

Mr. EGAN. Yes.

Mr. BURTON. Is it considered a toxic substance?

Dr. WHARTON. Yes.

Mr. BURTON. Do we still allow it to be put into thermometers? Do we put it into thermometers any more? I remember when we were kids, we didn't know better, we'd play with that mercury. Is it available like that any more?

Mr. EGAN. I actually don't know. I don't think I've seen them.

Mr. BURTON. The answer I think is no.

Mr. EGAN. I think they're in the water pressure rises, but I'm not sure.

Mr. BURTON. Well, that may be. I know I have a friend that works in the things that set the heat in your house, and they're going to try to get the mercury out of those, because it's toxic, and because they put it in landfills when they don't work and it gets into the water system and the water supply and it leaches into people through the water. And we just got the report from the Great Lakes, I think, that there are unsafe levels of mercury in our water.

So mercury is a toxic substance. And you keep talking about thimerosal. We're talking about mercury. Mercury is a part of the thimerosal. So when we talk about, when you give your testimony, I'd just as soon you say mercury instead of thimerosal. Thimerosal is a way to kind of cover up that it contains mercury.

What level is safe? You gave us an amount, Dr. Egan. What level is safe?

Mr. EGAN. I can only quote the different guidelines that have been put forth on the basis of the number of studies.

Mr. BURTON. What studies?

Mr. EGAN. That were conducted by the studies in the Seychelles, studies that were in the Faroe Islands, estimates from accidental mercury exposures.

Mr. BURTON. So what level is safe?

Mr. EGAN. Well, there are various levels for different purposes.

Mr. BURTON. Does it vary from person to person because of their ability to reject or live with it?

Mr. EGAN. Yes, there are certainly differences between people and between a developing fetus and a child.

Mr. BURTON. So there's really no real scientific evidence that says, this amount of mercury in a person's body is safe and this amount is not safe from person to person?

Mr. EGAN. Well, I guess, yes, the guidelines that the EPA got were 0.1 micrograms of mercury per kilogram of body weight per day.

Mr. BURTON. That's kind of subjective, though, isn't it? I mean, I don't understand how they came up with that.

Mr. EGAN. Well, from the studies that they did, looking for abnormalities or where, developmental abnormalities or behavioral abnormalities. And based on those ranging studies that were unfortunately the result of accidents and looking for what the damage of thimerosal was, they got this level which they said was a level, their reference dose, which is the dose that they felt——

Mr. BURTON. They felt.

Mr. EGAN [continuing]. Could be taken into the body every day over a lifetime with no observed effect.

Mr. BURTON. Has thimerosal ever really been tested? Has thimerosal ever been tested by our health agencies?

Mr. EGAN. Only in those early tests that you know of that were done by Lily.

Mr. BURTON. When was that? That was done in 1929. Let's followup on that. In 1929, they tested this on 27 people that were dying of meningitis. All of those people died of meningitis, so they said there was no correlation between their death and the mercury in the vaccines. That is the only test that's ever been done on thimerosal that I know of. Can you think of any other?

Mr. EGAN. No, in people, no. Except for accidental exposures over time.

Mr. BURTON. So we have mercury that's being put into people's bodies in the form of this preservative, and has been since the 1930's, and it's never been tested by our health agencies. And yet you folks come here and you testify that there's no conclusive evidence, and the IOM says, they favor, get this, they don't say they're sure, they say they favor rejection of a causal relationship between mercury and autism and other neurological disorders. Nobody ever gives a categorical statement, that no, mercury does not cause this, no, it doesn't. And that's because you can't do it.

So why in the world are we even putting a little bit of it in vaccinations? Why are we doing that? Why? Can't we create single shot vials of these various vaccinations that does not require mercury being put in them? Can we come up with another preservative, a way to preserve these vaccinations so they don't put the toxic chemical mercury into our bodies?

Mr. EGAN. I can't speak to finding another preservative. That's a very, very difficult issue. And I don't know if it's possible to find something that works as well to replace thimerosal. Tuthemoxyethanol seems to work in some cases.

Mr. BURTON. How about if you——

Mr. EGAN. We are diligently working, as we have testified today and previously, toward eliminating thimerosal mercury from vaccines as quickly as can be done. But there are many issues that are involved in doing this. If we were to say tomorrow that all vaccines, for example, all flu vaccines could only be administered in single dose syringes or single dose vials, the capacity to fill those does not exist.

Mr. BURTON. Well, you know, right now we have a new vaccine that's being tested on people below the age of 50 that doesn't contain thimerosal that you administer through your nose. It's not even a shot. Are you familiar with that?

Mr. EGAN. Yes, that's the vaccine that I spoke of.

Mr. BURTON. Does it contain mercury?

Mr. EGAN. No, that's thimerosal-free.

Mr. BURTON. Yes. So you can do it. Now, let me ask you, do we have a——

Mr. EGAN. And other manufacturers are working toward that, and have put out the vaccines that are thimerosal reduced.

Mr. BURTON. The vaccines that we have in the marketplace that are now thimerosal-free, do we have vaccines that were made with thimerosal that does the same thing that's still on the shelves that doctors are using?

Mr. EGAN. If I understand your question——

Mr. BURTON. In other words, there's a shelf life.

Mr. EGAN. Yes, are there any of the routinely recommended pediatric vaccines that should be on the shelf now, the answer is no. To the best of my knowledge, they've all gone past their expiration date.

Mr. BURTON. They've all gone past it, so there's none on the shelves?

Mr. EGAN. I was actually somewhat surprised with your opening comment, and I would certainly like to know——

Mr. BURTON. I've been told that there are some children's vaccines that are still being utilized that contain mercury that now are being produced mercury-free. And you're saying that's not so?

Mr. EGAN. Unless you mean trace amounts of thimerosal.

Mr. BURTON. Wait a minute, hold it. I don't want to monopolize this, I want to let my colleagues answer questions and we'll come back.

Mr. EGAN. But I would appreciate——

Mr. BURTON. What is a trace amount?

Mr. EGAN. We define that as meaning less than 1 microgram of mercury per dose.

Mr. BURTON. OK. Now, my grandson got nine shots in 1 day, seven of which contained mercury. So if he got the very small amount, he'd be getting maybe 9 micrograms, right?

Mr. EGAN. No, much less than that. Because the maximum that we calculate that a child could receive now during the first 6 months of life is somewhat less than 3. A number of these vaccines with defined trace as less than 1, some of them have considerably less than 1.

Mr. BURTON. But that amount of mercury would not do any neurological damage to anybody?

Mr. EGAN. Not according to any guideline.

Mr. BURTON. No, no, no, no. I want you to say yes or no.

Mr. EGAN. I do not believe so.

Mr. BURTON. You do not believe so. I didn't say believe. Can you say to me right now that amount of mercury being injected into a baby will not hurt it?

Mr. EGAN. It's impossible to make those categorical statements with 100 percent——

Mr. BURTON. That's right. So it is possible that the amount of mercury that's being injected, even in trace amounts, could damage a child neurologically, right?

Mr. EGAN. I don't think it has that capacity, no. We can argue.

Mr. BURTON. I know, but you don't think it is, but you can't say categorically, can you?

Mr. EGAN. Do I have evidence for every single child, for every possible dose, the answer is no.

Mr. BURTON. There you go. Let me yield to Ms. Watson, and I'd like to ask a few more questions after my colleagues ask questions.

Ms. WATSON. Thank you. In the State of California, we had proposition 65 a decade ago that the kinds of toxins that are available in the environment, and the goal of establishing the list was to be sure we diminish the risks that citizens are under by being exposed to these toxics. Mercury is at the top of the list, and I understand that WHO had an international ruling that mercury should come out of all thermometers.

Congressman Burton and I have sponsored H.R. 1618 to phase-out mercury-based fillings and to ban their use immediately for children and pregnant women. As far as can be determined, based on scientific evidence at this point that even trace elements can do harm in the fetus, and I understand mercury is biocumulative. So what are the safe dosages are, the safe amounts to use in dental amalgams or fillings? Can either one of the three, any of you respond?

Mr. EGAN. Unfortunately, we were not aware that this hearing was also going to go into dental amalgams, or else it would have been possible for us to have somebody from the Center for Medical Devices.

Ms. WATSON. Let's talk about mercury. Mercury's infusion into the body, what are the safe amounts? Do you have any idea?

Mr. EGAN. Well, the EPA guidelines where they said there should be no adverse effect if continuously received over a lifetime was 0.1 microgram per kilogram of body weight per day. That was designed to protect the developing fetus, which they felt, and I think rightly so, was much more sensitive to any potential harm. The ATSDR and FDA standards, guidelines are somewhat higher.

Ms. WATSON. If we know and we have empirical evidence that mercury is very toxic to the human body and to the environment, the exposure of mercury creates a real challenge for us, why is it that we don't eliminate it from all products that are ingested or used internally? And we have a whole different set of issues, the external, getting rid of mercury. Why is it that we still use trace amounts or larger amounts, thimerosal, why do we use it in other products? We'll just leave dental amalgams on the table for the time being.

Mr. EGAN. OK, thank you. Well, certainly for the vaccines and the use of thimerosal, we have been working diligently to remove thimerosal from these products as quickly as we can. It's not possible to do these overnight. If one wants to develop a process, a manufacturing process that's completely preservative free, one has to develop a new manufacturing process and validate it, present that data to FDA, have it reviewed.

If we talk about removing the thimerosal at the end, or not getting it, there are a number of issues about the quality of the product and the nature and quality of the product having done this. Data have to be generated and submitted to FDA and these need to be reviewed.

All of this switchover takes time. Moreover, the primary way that, you know, we haven't been able to find, or there aren't very good alternative preservatives, the non-mercury containing ones. So what people have done, the manufacturers have done, is primarily switch to single dose files or prefilled syringes, which do not require a preservative. The preservative is needed because you go into the vial many times, it can be bacterially contaminated and then you get bacterial infections. So it's to prevent that, that the preservative is there.

But switching over to these single dose vials, preservative-free, again requires validating that these can be filled aseptically. Because we don't want to create other problems. Moreover, the capacity to put these many doses of vaccines in these single does vials of syringes doesn't exist at the moment, although manufacturers are working toward that.

So we do have some vaccine out there now that's thimerosal-free. There was last year for the pediatric population. There is this year for the pediatric population. Much of it goes unsold. The uptake is not as high as I would like.

But we're working toward this goal in the face of these number of studies that say that there are no effects of thimerosal in vac-

cines on neurodevelopmental disorders. But because, as you and Chairman Burton have pointed out, it is a neurotoxin and we are, the public health service is committed to removing it whenever possible. As you said, and California has done——

Mr. BURTON. If the gentlelady would yield, the IOM report that was done that you quoted a while ago, weren't there five studies that they discounted, five studies they discounted that said that thimerosal was a contributing factor to neurological disorders, including autism?

Mr. EGAN. Well, they looked at all the studies that were——

Mr. BURTON. I'm just asking, weren't there five that they discounted from various sources that did conclude that autism was caused by the mercury in vaccine?

Mr. EGAN. I don't know if discounted is the right word to use. They looked at all the studies, some they felt I think were more credible than others. I think we'll need to have——

Mr. BURTON. Let me just say that there were five studies that did say there was a connection between the mercury and neurological disorders, including autism. There were five, they discounted those.

Thank you for yielding.

Ms. WATSON. Do you remember mercurochrome?

Mr. EGAN. Sure. We used it all the time.

Ms. WATSON. Yes, I did too, as a child.

Mr. EGAN. Every cut got it.

Ms. WATSON. How long did it take to remove it from the American market? I know you can get it in foreign countries. How long did it take to declare that mercurochrome was toxic and have it removed?

Mr. EGAN. That's something regulated by our Center for Drugs. I'll have to get back to you on the status of what that was, when it was removed and for what reason.

Ms. WATSON. We know the statutes, I just wanted to know the length of time. You don't have the answer so let me move on.

Mr. EGAN. Someone else would have to answer that for you.

Ms. WATSON. I don't know why the process takes so long, when we know, I mean, intellectual honesty tells us that mercury, if it is ingested, has a negative effect on the body. If we know that, why doesn't CDC or FDA move toward as quickly as possible trying to remove it from use? Anyone want to speculate on that?

Mr. EGAN. I'd be happy to take a shot. I think we are. And we, the CDC and the manufacturers——

Ms. WATSON. That gives me some hope.

Mr. EGAN. I think we've done pretty good with all the pediatric vaccines and now we're talking about flu. But as was mentioned before, this is a very devastating disease. Now——

Ms. WATSON. We're not talking about the disease. Let me ask the question. Can you respond why it's taking so long when we know the level of toxicity of mercury to have our leading agencies come out and say, our goal is to remove it from all these products?

Mr. EGAN. The first issue is, thimerosal is in there during the manufacturing process. I'll just talk about one of the companies. We need about 100 million doses of flu vaccine per year in the United States. Now, when they take the thimerosal out at the end,

they lose about 30 percent of that, a third of that. So that would mean that if we said we could only have the thimerosal-reduced vaccine, containing a trace, we would have much, much less vaccine available, maybe 70 million doses instead of 100 million doses.

The second issue is even if we had all of this thimerosal-reduced vaccine containing only the traces, they don't have the capacity at this time to put it into the single dose vials and syringes, so they couldn't get it out.

Ms. WATSON. Who doesn't?

Mr. EGAN. The manufacturers. They are addressing that, they are building new plants, new manufacturing suites. They are developing new manufacturing processes that don't require thimerosal in them. And we do have some of them now, the thimerosal-reduced vaccine out there. And as Mr. Burton just noted, we also have the inactivated, I'm sorry, the live attenuated vaccine, which has none.

And we are going there. But developing these processes and validating and building the plants and building the filling suites takes a considerable amount of time.

Ms. WATSON. My final question, where are the various agencies of Government that are involved in focusing on these products, what is your goal? What would you like to see? What would you like to promote, those of you that are involved? I think there are a set of facts already known about mercury as an ingredient in any substance, any product. What are you aiming for, what would you like to see?

Mr. EGAN. What I have been aiming for and what I would like to see is only thimerosal-free products, both for children and adults.

Ms. WATSON. Very good. Because you see, that helps me in terms of being a policymaker, knowing where we need to go. And if I know that we have our various agencies of Government with us, then it encourages us to continue down this same way. Thank you very much, Mr. Chairman.

Mr. BURTON. Thank you. Before I yield to my colleague, let me just say that I was chairman of the full committee for 6 years. I have now been chairman of this subcommittee for 2 years. That's 8 years. We've been talking about this since I first started as chairman, maybe 7 years ago.

All I can say is, I don't know how long it's going to take. I hope it happens in my lifetime. You're saying, well, you need to work toward that, for single shot vials, you need to work toward getting thimerosal out of these products, or mercury out of these products. We've been after this now for 8 years.

Now, progress is being made, but sometimes I feel like it's pulling a wisdom tooth, where they get into your mouth with both feet and both hands and they're in there jerking that tooth out and it's just so hard to get it moving. Eight years, 7 years should be long enough. The manufacturers, with the technology that we have today, the quantum leaps that are being made in technology and industry, it seems to me they could have made this changeover. I think the main reason is money and I think the main reason is because they're concerned about the liability factor.

Mr. Murphy.

Mr. MURPHY. Thank you, Mr. Chairman.

A few questions on some of the issues that were raised. Dr. Wharton, in your testimony you mentioned that for a period of time, only 61 to 66 percent of children would have received a vaccine for measles. Was that the whole MMR group that they would have received?

Dr. WHARTON. That was predominantly as MMR, that is generally the vaccine that was administered.

Mr. MURPHY. I'm sorry, I'm having trouble hearing you.

Dr. WHARTON. Yes, it is predominantly with MMR.

Mr. MURPHY. OK. Which means about a third of children did not receive them then. Was there a subsequent study which looked at that third that did not receive compared with the two-thirds that did receive it to see if there was a difference in incidence of autism related disorders?

Dr. WHARTON. During the period of time in which preschool immunization coverage was low in the United States, most children did receive measles vaccine prior to school entry. So it wasn't that the children remained unvaccinated forever, they simply weren't vaccinated in a timely way.

There have been a couple of studies done which have looked at differences in autism among MMR vaccinated and unvaccinated populations. In a study in Denmark, no difference was found in the rate of autism among children who received MMR vaccines compared to those who hadn't. Our birth defect center also did a study looking predominantly at the timing of administration of MMR since again most children do receive the vaccine prior to school entry. There was no association found, there was not found to be a difference.

Mr. MURPHY. Dr. Boyle and Dr. Egan, do you agree with that?

Dr. BOYLE. Essentially the study that we did in our birth defects center indicated that there was no relationship between timing of the administration of MMR vaccine and autism.

Mr. MURPHY. What I'm concerned about here is you have groups here that, even if you have 90 percent of children getting it, you open up the issue that some children did not and some children did. Was there actually an epidemiological study which looked at children who never received any of these things? Is there a clinically, not just statistical, but clinically significant difference in autism spectrum disorders?

Dr. BOYLE. In our Denmark study, there were children who were not vaccinated at the time of followup, and there was not. So that's probably the closest one.

Mr. MURPHY. The next question I have relates to maternal exposure. If mother has had exposure to mercury herself, either fillings or her vaccinations, etc., does that mercury accumulate in her system and is that passed on to her fetus?

Mr. EGAN. Maybe I can comment a little bit on what I know. This is not complete. There is mercury that will go to the developing fetus. That's why the EPA set their guidelines so low, to protect the developing fetus.

The second thing is that mercury is excreted.

Mr. MURPHY. So it does not remain—there are a couple of things here and I understand EPA is looking at substances, fish and other

foods a mother may eat during pregnancy. But I'm wondering, if she had been exposed when she was a child, and things she ate, even if she stopped before pregnancy, does mercury accumulate in her system and is that passed on, even if that baby never was exposed to mercury, will the substance be passed on through her, from her own childhood?

Mr. EGAN. I don't know the whole pharmaco——

Mr. MURPHY. I only want you to speak to what you scientifically can verify.

Mr. EGAN. I don't know, sir.

Dr. WHARTON. I know that we are doing some work in our National Center for Environmental Health on this issue in terms of looking at actual exposures from elemental mercury, which would be mercury from amalgams.

Mr. MURPHY. OK. And this is where we raise the question, if there was a link between mercury, that if there was some that she has from amalgams or from her own childhood, too, that could be important for us to find out if there are links there. Is it safe to say we don't know this yet?

Dr. WHARTON. I would say it's safe to say we don't know. We're conducting a very large study in a number of areas in the country and that would be one of the issues to address, those environmental sources of mercury, as well as medical sources.

Mr. MURPHY. Would that then confuse or confound any ability to draw conclusions then from what I mentioned before, that if there were children that did not receive MMRs and those that did, I'm wondering if it would confuse the results, being able to clearly delineate distinctions between those children who did or did not have autism spectrum disorders based upon exposure to mercury during immunizations?

Dr. WHARTON. Well, it is true that in many epidemiologic studies you're unable to completely account for these other sources of exposures, because they're very difficult to quantify or estimate, things that happened previously. But in order for it to influence the results of the study, the exposure needs to be different in the vaccinated and the unvaccinated group, if it's randomly allocated it really shouldn't affect the results much. And there is not any particular reason to think that those exposures would have been different among for instance, those families who vaccinated or did not vaccinate their child.

Mr. EGAN. You've all testified to the point that mercury is being removed from many vaccinations, so now there are more and more children being vaccinated with virtually no immunization exposure to that. That's only a couple of years old now? How long has it been, in 2003 I think it was?

Mr. EGAN. Well, this started in 1999, when Merck produced the hepatitis B vaccine that's given at birth, that they came out with their thimerosal-free version. Then in March 2000, GlaxoSmithKline, their versions of thimerosal-reduced. And these have been phasing in since 1999. You're correct, it's been the last couple of years where it's been completely free. But it started decreasing in 1999, 2000, 2001.

Mr. MURPHY. I know from my own clinical practice as a psychologist sometimes you can begin to detect autism spectrum disorders

very early in a child's life, one and a half or two in some cases, even younger. And some children you need to do it at later ages, 4, 5, 6, etc., for the higher functioning Asperger's types. Is someone conducting these studies now, following up these children, and do we have any preliminary results?

Dr. BOYLE. I would testify to the actual studies that we've done specifically to address vaccines in the center that I'm in, which is the National Center for Birth Defects and Developmental Disabilities, where we're doing, as I mentioned before, a very large study to look at a number of different exposures. It would be vaccines but also maternal and other early life exposures.

Mr. MURPHY. We'll be waiting for those results, then.

Thank you, Mr. Chairman.

Mr. BURTON. Thank you, Representative Murphy. I just want to ask a couple more questions, then I'll let you go. First of all, I'm sure you read the Wall Street Journal article yesterday.

Mr. EGAN. Yes, I actually did see that.

Mr. BURTON. Did you get a chance to read that?

Mr. EGAN. I saw the article.

Mr. BURTON. That's good. We have people who will be testifying today that worked on those studies, which show problems with mercury in mice, administered in similar doses to human beings in a relatively consistent way. You said mercury is excreted?

Mr. EGAN. Yes.

Mr. BURTON. A lot? Because we were told by scientists who have been before this committee from around the world that mercury has a cumulative effect in the brain, it gets into the fatty tissues in the brain and it is difficult for it to be excreted once it gets into the brain and it has a cumulative effect.

Mr. EGAN. Yes, there is some accumulation, some——

Mr. BURTON. So it isn't all excreted. So if you get a whole bunch of shots, like if children get as many as, or were getting as many as 25 to 30 shots before they started to school, the mercury would accumulate even though some of it is excreted, right?

Mr. EGAN. You know, in the absence of any additional exposures, I don't know that it's not actually all excreted. The study the people did showed half times for ethylmercury, it was around 7, 8 days, and for methylmercury it was around 30, 40 days. Those are the times at which half are eliminated. If there is some fraction that remains, I don't know.

Mr. BURTON. Some others that we've had, other scientists from around the world who testified before the committee, it's not a fraction, it's a substantial amount. The Denmark study, you keep referring to that Denmark study. The Denmark study, according to many of the experts that we've had before the committee, not you folks, but many of the experts say that is a flawed study, and there were 14 different studies that the IOM used to come up with their last analysis. Five of the studies, not of the 14, but 5 additional studies were discounted.

But one they laid an awful lot of the interest in was the Denmark study. And scientists that we've had before this committee say that that Denmark study is very, very flawed for a number of reasons. So referring to that over and over again I don't think really proves much.

I do want to ask, if you get a chance, I know you have busy schedules, we're going to have the people testify here at the next panel who have worked on these new studies. I think it would be beneficial, if you had the time, to hear some of their testimony. Would you have the time to listen to those folks, or do you folks have to leave?

Mr. EGAN. I think we have to get back.

Mr. BURTON. Do you really? Gosh.

Mr. EGAN. But certainly we can read the testimony. We're reading the papers.

Mr. BURTON. I know. I realize that their studies are really not that significant or important.

Mr. EGAN. No, that's not true.

Mr. BURTON. That's not so?

Mr. EGAN. No.

Mr. BURTON. Well, they're not so significant that you guys can't stay around here like we do and listen to them and glean from them some of the information. But I'll make sure that you get copies of them. And I'll send you, if you don't mind, a raft of questions about their studies that I hope you'll answer. Would you be willing to answer those questions for us when we send those to you?

Mr. EGAN. Yes.

Dr. WHARTON. We will be happy to do that.

Mr. BURTON. Would you be happy to do that? Then I have one more question and I'll let you go. The hepatitis B vaccination is given to children at birth. And this has nothing to do with the mercury content. As I understand it, you can only get hepatitis B from blood, needles or some direct contact with a person that has hepatitis B, is that correct?

Mr. EGAN. Yes. To the best of my knowledge.

Mr. BURTON. Why are we giving hepatitis B vaccination to a child the minute they come out of the womb? They're not exposed to needles from drugs. They're not exposed to blood products, other than from the mother and other bodily fluids from the mother. So why do we do that? I'm not saying that you shouldn't give that hepatitis B vaccination, I just wonder why you're doing it at birth.

Mr. EGAN. I'm going to have to let CDC answer.

Mr. BURTON. Why is that?

Dr. WHARTON. There's a couple of reasons for it. Perhaps the most salient is that we have an imperfect system for ensuring that we can protect newborn children from transmission of hepatitis B virus from the mother at the time of birth. Some women are not tested during pregnancy to determine whether or not in fact they are contagious to their child for hepatitis B virus. In some events you are tested, the results are not communicated to the birth hospital.

We know we can prevent perinatal transmission of the hepatitis B virus by timely vaccination and administration of hepatitis B immunoglobulin. In the absence of knowledge of the mother's status, we can still prevent many cases by that newborn immunization. Children who are infected with hepatitis B virus at birth have a high risk of establishing chronic infection, permanent hepatitis B disease, or should they survive, long term risk of liver cancer. In order to, because we are not able to assure that every child who

is born to a hepatitis B surface antigen mother is known at the time of birth, the routine hepatitis B immunization program provides a safety net.

Mr. BURTON. Well, I understand what you said, it just seems to me that between the time they're born and the time they go to school might be a good time to give it. I just never have understood why they do it at birth. And it does include mercury still, hepatitis B still does contain mercury?

Mr. EGAN. The vaccine that's produced by Merck, the Combivax HB, that is completely free of mercury. The Comvax, which is the hepatitis B-HIB conjugate comvaxes vaccine, is also completely free of mercury thimerosal. The InterexB, which is manufactured by GlaxoSmithKline, does contain a residual trace of mercury and it's somewhere on the order of about 0.05 micrograms——

Mr. BURTON. If you have some that don't include it, why not get the mercury out of all of them? Anyhow, that's something that you can look into later.

Mr. EGAN. They actually are trying to develop those.

Mr. BURTON. OK. We have a vote on the floor, Representative Murphy, so we will stand in recess until the fall of the gavel. We'll be back here in about 10 minutes. Thank you very much for your testimony. And I will send you copies of the testimony of the people that are going to be testifying on these other studies. I really hope you will respond to the questions we'll ask along with those studies.

We stand in recess until the fall of the gavel.

[Recess.]

Mr. BURTON. The subcommittee will come to order.

Our next panel consists of Richard Deth, Ph.D, from Bouve College of Health Sciences, Department of Pharmaceutical Services, Northeastern University; Marcelle Joust, Ph.D., D.O., health professor of psychology, director of the Center for Cognitive Brain Imaging at Carnegie Mellon University; Richard Fischer, DDS, International Academy of Oral Medicine and Toxicology, Annandale, VA, my good buddy who takes care of my teeth and makes me look halfway decent, which isn't easy; and Lynn Redwood, R.N., MSN, president of SafeMinds.

Would you please stand so you can be sworn?

[Witnesses sworn.]

Mr. BURTON. Thank you. According to my expert here, he says we should start with Richard Deth. So Dr. Deth, would you like to start? And if we could, I know that you're probably going to go over, but if you could keep your comments close to 5 minutes, I'd really appreciate it.

STATEMENT OF RICHARD DETH, PH.D., BOUVE COLLEGE OF HEALTH SCIENCES, DEPARTMENT OF PHARMACEUTICAL SERVICES, NORTHEASTERN UNIVERSITY

Mr. DETH. I'll do my best, thank you. And thanks to you, Chairman Burton, for the opportunity to testify today about our thimerosal-related research that we do at Northeastern and its significance for autism and understanding autism.

At the outset, I have to say that there is indeed a molecular cause for autism. As a result of it being molecular, you're going to

have to tolerate my talking about molecules for the next 5 minutes here. I trust you'll forgive me for that.

The primary goal of my research, that of my close collaborative colleagues, is to find the cause of autism so that we can use this information to identify effective treatments for autistic children. I'm pleased to say that we've made progress on understanding the disease and also on the treatment.

The molecular problem at the heart of autism appears to be a process known as methylation. Methylation means the transfer of single carbon atoms or methyl groups between molecules. And this process is highly sensitive, as it turns out, to heavy metals, and it also turns out to be particularly sensitive to thimerosal.

At the heart of the methylation process is the methionine cycle shown in this slide here. Our lab has been studying the role of methylation in mental illnesses. Methyl groups are brought to this methionine cycle that is at the bottom of this slide by the folate pathway, that's shown at the top of the slide. The key enzyme that brings the methyl groups to the pathway is called methinionine synthase. A methionine synthase requires vitamin B12 to bring the methyl groups, and as it turns out, thimerosal potently inhibits methionine synthase. We published this this past April in the Journal of Molecular Psychiatry.

The inhibition by thimerosal occurs at concentrations easily produced in the blood of children after even a single vaccination, as shown in this slide by the arrow. Now, we now know that thimerosal inhibits this enzyme, methionine synthase, by blocking the formation of the active form of vitamin B12, which is known as methylB12 or also as a methylcobalimin.

The next slide just outlines the pathway here and what it shows is that cobalamin or B12 forms that we take in either by the diet or from vitamin pills have to first be converted to active methylB12 before they can be used. And as summarized in my written testimony more extensively, thimerosal blocks the first step in this synthesis of methylB12, and as a result, it inhibits methylation.

In neuronal cells, methylation can be stimulated by the neurotransmitter dopamine. This appears to be important for normal attention and the capability for normal attention. Thus, ADHD, attention deficit hyperactivity disorder, and autism are manifestations of what happens when methylation is impaired in the brain.

Recently, Dr. Jill James measured the blood levels of methionine cycle metabolites in children with autism. As illustrated in this table, all the levels of these metabolites were abnormal, confirming that methylation is indeed impaired in autism. Her work will be published shortly in the American Journal of Clinical Nutrition.

During the last year, researchers that I collaborate with have examined genes that regulate methylation, and they have found that autistic children have a significantly higher frequency of so-called disabling polymorphism or mutations in these genes. The next slide summarizes some of these genes. Thus it appears that a sub-population of children who carry these genetic risk factors are more sensitive to the toxic effects of thimerosal and therefore are at greater risk of developing autism.

The next slide shows some data that we recently obtained in what I call a Timmy and Tommy study. That is in the same family, two siblings, Timmy and Tommy, one developed autism and one didn't. We had the opportunity to study the cells from such individuals, and what we have found is that the individual that developed autism is the one that was more sensitive to thimerosal as shown in this illustration.

The good news that goes along with the knowledge of this mechanism is that metabolic interventions which augment methylation are proving to be effective treatment for autism. These treatments include methylB12 itself, which can produce dramatic improvements in some kids, as first reported by Dr. James Neubrander. In other words, thimerosal is a toxin that inhibits methylB12 synthesis. This lists some of the treatments. Thimerosal is a toxin that inhibits methylB12 synthesis, and giving methylb12 turns out to be an antidote for this toxin.

While further work is needed to identify the optimum treatment for autism, these early clinical findings are encouraging.

In conclusion, it appears that thimerosal causes autism and ADHD by interfering with folate dependent methylation by the enzyme methionine synthase. And it does this by blocking the synthesis of methylB12, the active form of B12. Genetic risks in the form of polymorphism and methylation related genes increases thimerosal toxicity in some children. And the fact that methylation enhancing metabolic treatments improves autism provides strong evidence that impaired methylation does indeed cause autism and that increased thimerosal exposure has been the critical factor in this so-called autism epidemic.

So what caused the autism epidemic would be, the 1 in 10,000 frequency that was observed in 1970 is now, as we've heard today, 1 in 162. That difference is not due to changes in genetic risks, but due to an increase in exposure to thimerosal.

I thank the chairman and others for their attention and look forward to your questions. Thank you.

[The prepared statement of Dr. Deth follows:]

Molecular Aspects of Thimerosal-induced Autism

Richard C. Deth, Ph.D.
Professor of Pharmacology
Northeastern University
Boston, Massachusetts

Summary

The developmental disorder autism has both genetic and environmental origins, and its forty-fold increase during the past two decades reflects an increased role for environmental factors. It has been proposed that increased use of vaccines containing the ethylmercury derivative thimerasol is the major contributing factor. Published research from my laboratory has revealed that thimerosal is an exceptionally potent inhibitor of biochemical pathways that transfer single carbon atoms between molecules. These "methylation" pathways are critically involved in several important functions including the regulation of gene expression and the molecular mechanism of attention. Recent studies from my lab indicate that thimerosal exerts its toxic effect on methylation by interfering with formation of the active form of vitamin B12, also known as cobalamin. Dietary B12 must be converted to methylB12 (methylcobalamin) in order to assist in the transfer of single-carbon methyl groups from the folic acid pathway by the enzyme known as methionine synthase. By reducing methylB12 formation, thimerosal inhibits this enzyme and thereby interferes with methylation events. Autistic children have abnormal plasma levels of methylation-related metabolites and exhibit higher frequencies of genetic mutations that affect this pathway. These genetic risk factors make them less able to detoxify thimerosal and also increase their sensitivity to its mechanism of toxicity. In many cases, autism can be effectively treated by the administration of methylB12 along with other agents that augment methylation capacity. Taken together, these facts indicate that increased exposure to thimerosal has combined with genetic risk factors in a sensitive subpopulation to cause the recent rise in autism.

Outline

1. The Puzzle of Autism

Autism is a pervasive developmental disorder characterized by deficits in language, attention, cognition and learning, frequently accompanied by abnormal

behavior including social isolation, repetitive activity and emotional lability. Severe deficits may be recognized at birth, but a failure to achieve standard milestones during initial years of life remains the primary basis of diagnosis in most cases. While the underlying cause(s) remains obscure for many developmental disorders, metabolic abnormalities (e.g. Lesch-Nyhan Syndrome and adenylsuccinate lyase deficiency) or impaired methylation-dependent gene silencing and/or imprinting (Rett and Fragile-X Syndromes) (1-4) suggest biochemical mechanisms that may be involved. Development disorders can also be caused by exposure to toxins (e.g. ethanol, in fetal alcohol syndrome; heavy metals, in lead poisoning) (5,6), although the precise molecular mechanisms underlying their toxicity are not known. The recent increase in the incidence of autism has led to speculation that environmental exposures including vaccine additives (i.e. aluminum and the ethylmercury-containing preservative thimerosal) might contribute to the triggering of this developmental disorder (7).

Based upon a high concordance in twin studies, genetic factors are thought to play an important role in causing autism. However, it is clear that the recent dramatic rise in autism rates is not caused by a genetic phenomenon. The more likely scenario is that autism is caused by the interaction of genetic risk factors with environmental risk factors and the importance of the environmental factors has increased during the past twenty years. As illustrated in Fig. 1, the "Puzzle of Autism" therefore is the challenge of understanding exactly which genes provide the inborn risk, and which environmental factor(s) is serving as the trigger. The molecular mechanism at the intersection of genetic and environmental factors should be capable of accounting for the observed symptoms of autism, and knowledge of this mechanism should help identify effective treatments for

autism. The findings summarized in this report indicate that impairment in the biochemical pathways that allow for the transfer of single carbon groups (i.e. methylaion) is a major factor contributing to the cause(s) of autism.

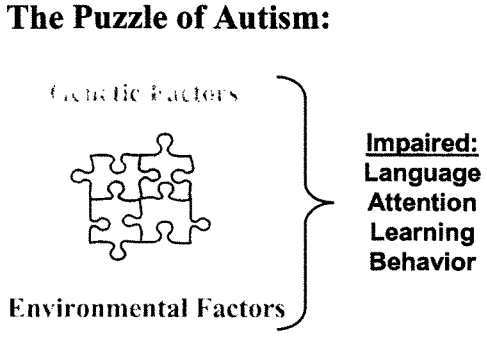

Figure 1: Autism is caused by a combination of predisposing genetic factors and environmental factors that synergize with each other to cause the symptoms that are typical of this developmental disorder.

2. Physiological and Biochemical Roles of Methylation

Methylation is the process by which a single carbon atom is transferred from a methyl donor to another molecule, commonly resulting in a change in the functionality of the recipient molecule. This seemingly mundane biochemical event is vital to life and to the normal capacities of developed organisms, including man. Perhaps the most important example of methylation is the epigenetic regulation of gene expression by DNA methylation. When DNA is methylated, gene expression is suppressed, and at any one time only a portion of genes are "on" with the others being turned "off". Since all cells possess the same DNA, differences between cell types (e.g. neurons *vs.* heart muscle *vs.* liver cells) are due to specific patterns of DNA methylation that characterize each type. Development begins with undifferentiated cells (i.e. stem cells) that gradually assume the characteristics of their final destiny as guided by sequential shifts in their

DNA methylation. Based upon this perspective, it is easy to see how abnormal methylation could alter the pathway of normal development and could contribute to neurodevelopmental disorders such as autism. Indeed, abnormal DNA methylation has previously been implicated as an important causative factor in Rett and Fragile-X syndromes (3,4)

As illustrated in Fig. 2, the major methyl donor in biological reactions is S-adenosylmethionine (SAM), an activated form of the essential, sulfur-containing, amino acid methionine. After donating its methyl group, the residual portion of SAM, S-adenosylhomocysteine (SAH), serves as a regulator of methylation by competing with SAM and inhibiting its methyl donation. The concentration ratio of [SAM]/[SAH] therefore reflects the potential for methylation, and any increase in [SAH] or decrease in [SAM] will lower methylation. As described below, children with autism have low levels of SAM and elevated levels of SAH, indicating an impaired potential for methylation. Methylation of neurotransmitters such as dopamine and serotonin terminates their signaling activity, which may also play a role in autism.

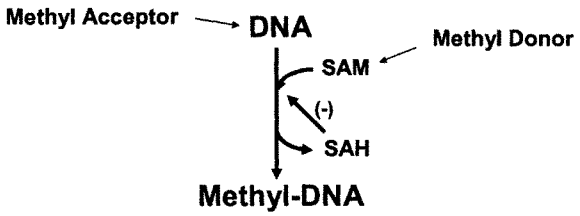

Figure 2: DNA methylation is carried with S-adenosylmethionine (SAM) serving as the methyl donor. The resulting S-adenosylhomocysteine (SAH) inhibits methylation by competing with SAM.

Availability of the methyl donor SAM is critical for methylation. SAM is formed by addition of an adenosyl group from the high energy molecule ATP to methionine, as a

part of the methionine cycle illustrated in Fig. 3. After methyl donation the adenosyl group is removed from SAH, in a reversible reaction yielding homocysteine (HCY) and adenosine. Any unusual build-up of adenosine can shift this reaction backwards toward SAH formation, while lowering HCY levels. As described below, this occurs in many children with autism. Activity of the vitamin B12-dependent enzyme methionine synthase converts HCY back to methionine, using a methyl group from the folate pathway.

METHIONINE SYNTHASE AND THE METHIONINE CYCLE

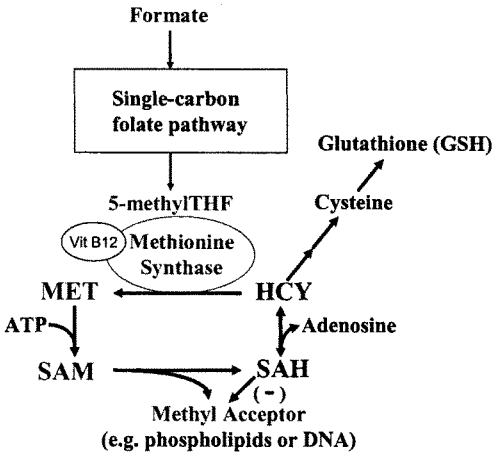

Figure 3: The four-step methionine cycle involves activation of methionine (MET) by ATP-dependent adenosylation, methyl donation by SAM, reversible dissociation of SAH, and remethylation of homocysteine (HCY) to MET by the vitamin B12-dependent enzyme methionine synthase, using methylfolate (5-methylTHF) as the methyl donor. HCY can alternatively be converted to cysteine and glutathione.

The methionine cycle is also involved in the ability of the neurotransmitter dopamine to stimulate methylation of phospholipids in the neuronal membrane. This

unique process was only discovered several years ago and its precise function remains unclear at this time. However, dopamine-stimulated phospholipid methylation (PLM) appears to be involved in the molecular origins of attention. Genetic variations in the D4 subtype of dopamine receptor that carries out PLM have been linked to attention-deficit hyperactivity disorder (ADHD) (8), and the ADHD-linked variant form is weak in its ability to carry out methylation (9). Impaired attention is a cardinal symptom of autism, and it is possible that this reflects reduced activity of dopamine-stimulated PLM. During dopamine-stimulated PLM, a methionine that is an integral part of the D4 receptor protein is converted to SAM, then SAH, then HCY and back to methionine again, as in the methionine cycle of Fig. 3. Thus enzymes in the methionine cycle, such as methionine synthase, actually have two substrates, one being a small individual amino acid, and the other being the large D4 dopamine receptor protein.

3. Activity of Methionine Synthase

Methionine synthase is situated at the intersection of the single-carbon folate pathway and the methionine cycle (Fig. 3), and is therefore well-positioned to regulate methylation. Its activity serves to maintain a low level of HCY, limiting its backward conversion to SAH and thereby promoting methylation. In a recently published study (10), we showed that methionine synthase activity in cultured human neuronal cells is substantially stimulated by both dopamine and insulin-like growth factor-1 (IGF-1) (Table 1). IGF-1 mediates many of the effects of growth hormone and is a key regulator of development, as well promoting neuronal myelination.

The mechanism of methionine synthase activation involves an intracellular signaling pathway, the PI3-kinase pathway, commonly activated by many different

cellular growth factors, including those that promote cellular differentiation and development. In subsequent investigations we found that methionine synthase activity in neuronal cells is absolutely dependent upon the ability of this signaling pathway to promote the formation of the biologically active form of vitamin B12 (i.e. methylB12 or methylcobalamin). It is pathway that is inhibited by thimerosal.

METHIONINE SYNTHASE ACTIVITY[1]

Treatment	pmol/min/mg
Basal	28.5 ± 4.3
IGF-1 (10 nM; 30 min)	62.2 ± 2.8
Wortmannin (100 nM; 60 min)	not detectable
IGF-1/Wort.	not detectable
Dopamine (10 μM; 30 min)	76.0 ± 3.7
Dopamine/Wort.	0.9 ± 1.2
Dopamine/IGF-1	132.1 ± 7.7
Ethanol (0.1%; 60 min)	not detectable
IGF-1/Ethanol	1.0 ± 1.3
Dopamine/Ethanol	not detectable
$HgCl_2$ (1 μM; 60 min)	not detectable
IGF-1/$HgCl_2$	not detectable
Dopamine/$HgCl_2$	not detectable
$PbNO_3$ (1 μM; 60 min)	2.6 ± 1.5
IGF-1/$PbNO_3$	37.9 ± 2.9
Dopamine/$PbNO_3$	26.3 ± 3.1
Thimerosal (10 nM; 60 min)	not detectable
IGF-1/Thimerosal	not detectable
Dopamine/Thimerosal	not detectable

Table 1: Effects of various agents on methionine synthase activity in neuronal cells. IGF-1 and dopamine stimulate activity, while the PI3-kinase inhibitor wortmannin, ethanol, mercury ($HgCl_2$), lead ($PbNO_3$) and thimerosal inhibit activity.

In the diet we take in vitamin B12 as its hydroxyl derivative, hydroxycobalamin, which must be subsequently converted to methylcobalamin before it can function. Dietary vitamin supplements provide cyanocobalamin, which again must be converted to methylcobalamin. Conversion to methylcobalamin can occur either directly in the

enzyme methionine synthase itself, or via the pathway outlined in Fig. 4. As illustrated, methylcobalamin synthesis requires glutathione (GSH) and SAM, and levels of each of these metabolites are reduced in autistic children (see below). Although additional studies are needed to clarify details, growth factors apparently augment synthesis of the intermediate glutathionylcobalamin, which is subsequently converted to methylcobalamin. The resultant higher level of methylcobalamin increases methionine synthase activity, lowering HCY and SAH levels and increasing methylation. In support of this mechanism, our published study showed that IGF-1 and dopamine increase the methylation of both DNA and membrane phospholipids in conjunction with their activation of methionine synthase.

BIOSYNTHESIS OF ACTIVE METHYLCOBALAMIN

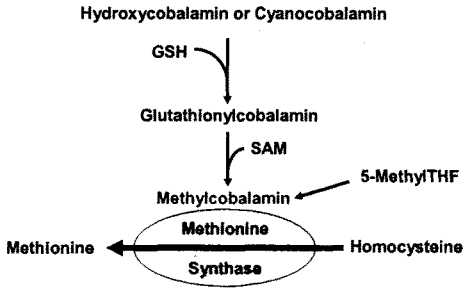

Figure 4: Dietary or multivitamin forms of vitamin B12 (cobalamin) must be converted to the active methylcobalamin form via a two-step process requiring glutathione (GSH) and SAM.

As illustrated in Fig. 5 (left), methionine synthase normally contains four domains: 1. A cobalamin-containing catalytic domain. 2. A methylfolate-binding domain. 3. A HCY-binding domain. 4. A SAM-binding domain. During the catalytic cycle, folate and HCY domains alternatively interact with the cobalt ion in cobalamin, which

alternates between Cob(I) and methylated Cob(III) states. Cob(I) is, however, extremely unstable, and occasionally it oxidizes to the Cob(II) state, interrupting folate-dependent HCY methylation. Oxidation is especially likely when levels of methylfolate are low and the Cob(I) state has to wait too long to receive a methyl group. Under this circumstance, the SAM-binding domain, when present, carries out a reductive methylation of Cob(II), with the auxiliary assistance of methionine synthase reductase. Thus the SAM-binding domain rescues oxidized cobalamin, allowing methionine synthase activity to resume. Alternatively, oxidized Cob(II) can be replaced with a new molecule of methylcobalamin to restart the enzyme. Thus oxidized cobalamin can either be repaired or replaced, but replacement places a high demand on methylcobalamin synthesis.

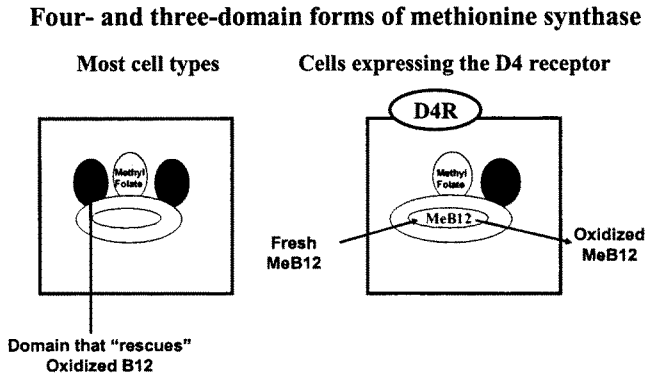

Figure 5: Methionine synthase can exist in both four-domain and three-domain forms. In the three-domain form, the SAM-binding domain that rescues oxidized Cob(II) is missing. In cells containing only the three-domain form, oxidized B12 must be replaced with methylB12 to resume enzyme activity.

In very recent and as yet unpublished studies, we have found evidence indicating that methionine synthase also exists with only three domains, with the SAM-binding domain being absent (Fig. 5, right). This form of the enzyme lacks the ability to rescue oxidized cobalamin, and therefore is highly dependent upon the availability of

methylcobalamin to sustain activity. As such, this form of the enzyme is subject to regulation by growth factors and the PI3-kinase signaling pathway, since they control the level of methylcobalamin synthesis. The particular human neuronal cell line we utilized contained only the three-domain enzyme. As a consequence, its methionine synthase activity and its methylation activity were tightly and completely under the control of the growth factors signaling pathway.

What would be the advantage to a cell of having a form of methionine synthase that could not repair its oxidized cobalamin co-factor? While we do not conclusively know the answer to this question, we hypothesize that the absence of the SAM-binding domain may improve the ability of the enzyme to utilize the D4 dopamine receptor as a substrate, since it is a larger, more bulky substrate than HCY, and the three-domain form is more prominent in cells expressing the D4 receptor. If correct, this would imply that the synthesis of methylcobalamin is of particular importance in those neuronal cells that express the D4 receptor. Moreover, toxic agents that impair methylcobalamin synthesis would particularly affect the methylation function of D4 receptors, and would therefore cause impaired attention.

4. Effects of Thimerosal and Heavy Metals

As described in our published study, a number of neurodevelopmental toxins share the ability to potently inhibit methionine synthase activity and methylation. These include ethanol, which causes fetal alcohol syndrome, heavy metals such as lead, which causes lead poisoning, as well as mercury and thimerosal. Fig. 6 illustrates the dose-dependent inhibition of phospholipid methylation (PLM) by lead and mercury. It is of particular note that concentrations of lead that reduce cognitive function (IQ) (6)

significantly inhibit PLM. Thimerosal, which releases ethylmercury, was more than 100-fold more potent than inorganic mercury at inhibiting methylation (Fig. 7). Ten days after vaccination with a thimerosal-containing vaccine, the concentration of ethylmercury in blood is reported to be approximately 8 nM (11). In our study, this concentration produced greater than 50% inhibition of methylation. Assuming that these blood levels are also present in the brain, one could reasonably expect that vaccine-derived doses of thimerosal inhibit methylation in the brain.

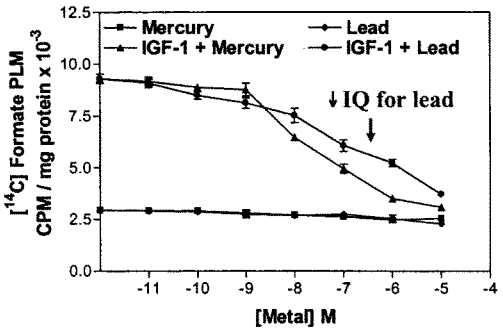

Figure 6: Mercury and lead potently inhibit the ability of IGF-1 to stimulate phospholipid methylation in human neuroblastoma cells.

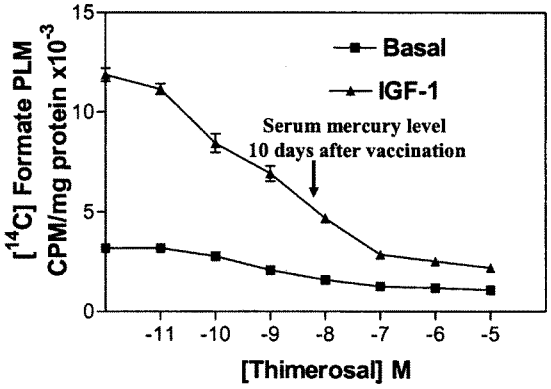

Figure 7: Thimerosal potently inhibits IGF-1-induced phospholipid methylation. Blood levels found in children ten days after vaccination produced approximately 50% inhibition.

Thimerosal, ethanol, mercury and lead also inhibited methionine synthase activity. As shown in Table 1, enzyme activity (i.e. methylation of HCY) was undetectable after a 30 min pretreatment with a thimerosal concentration close to the blood level found after vaccination (10 nM). Thus inhibition of methionine synthase accounts for the inhibitory effect of thimerosal on methylation. The toxic effect of thimerosal was also evident simply by observing the shape of cells, which changed from their usual spindle shape to a condensed, round shape (Fig. 8).

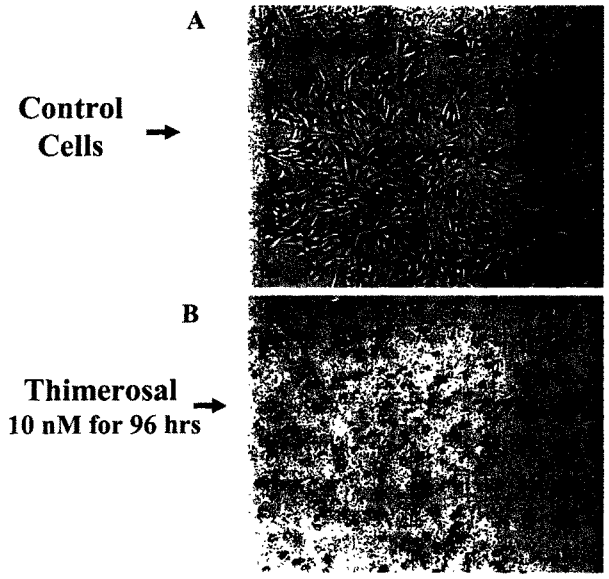

Figure 8: Thimerosal induces a dramatic change in the morphology of human neuroblastoma cells.

We further investigated the mechanism by which thimerosal inhibits methionine synthase. As shown in Fig. 9 (bottom), when enzyme activity was measured in the presence of either hydroxycobalamin or cyanocobalamin, thimerosal caused almost complete inhibition, however in the presence of methylcobalamin, thimerosal caused no

inhibition. Furthermore, when activity was measured in the presence of glutathionylcobalamin and SAM, thimerosal inhibition was again absent, although when SAM was not added, inhibition was observed. This pattern indicates that thimerosal inhibits the availability of glutathionylcobalamin, and that this action is responsible for its inhibition of methionine synthase and methylation.

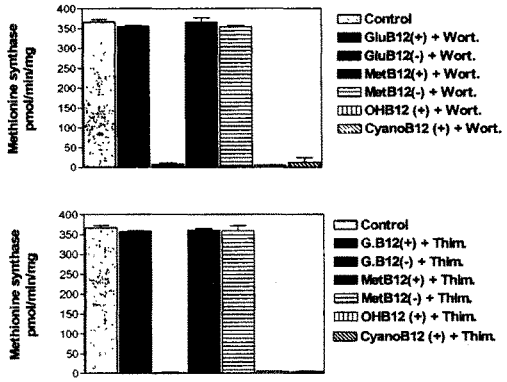

Figure 9: The PI3-kinase inhibitor wortmannin and thimerosal eliminate the ability of hydroxo- and cyanocobalamin to support methionine synthase activity. The presence of SAM is indicated by (+).

We also examined the ability of different cobalamins to support methionine synthase activity after inhibition of PI3-kinase. Treatment with the selective PI3-kinase inhibitor wortmannin caused a pattern of absolute dependence on methylcobalamin or its synthesis (gluthionylcobalamin + SAM) that was identical to the effect of thimerosal (Fig. 9, top). Since thimerosal and wortmannin produce identical effects, this data strongly suggests that thimerosal acts by inhibiting the PI3-kinase signaling pathway. **This is the likely mechanism by which thimerosal causes autism, and may also be the molecular basis for its toxic effect on bacteria, fungi that makes it an effective preservative.**

5. Autism-associated Metabolic and Genetic Abnormalities

Metabolic and genetic studies of autistic subjects provide a more complete view of how thimerosal, as an environmental insult, causes autism. Some of the most compelling information has only recently been obtained, and we are all indebted to the ongoing work of Jill James, Jeff Bradstreet, Marvin Boris, Alan Goldblatt, Ted Page, Gene Stubbs and others.

As described in a recent study by Dr. Jill James (12), the concentration of each of the individual metabolites in the methionine cycle and the trans-sulfuration pathway leading to glutathione synthesis is significantly abnormal in autistic children as compared to normal controls (Table 2). Notably, methionine and SAM levels are low, consistent with lower activity of methionine synthase. While a low HCY level might not be expected, the elevated levels of both SAH adenosine indicate that HCY is being drawn backwards toward SAH via the reversible activity of the enzyme SAH hydrolase. Thus an elevated level of adenosine restricts the availability of HCY for both methionine (and SAM) synthesis and for the formation of cysteine and glutathione.

	Control Children n=33	Autistic Children n=20	p value
Methionine (μmol/L)	30.6 ± 6.5	19.3 ± 9.7	0.001
SAM (nmol/L)	90.0 ± 16.2	75.8 ± 16.2	0.01
SAH (nmol/L)	20.1 ± 4.3	26.1 ± 5.4	0.001
Homocysteine (μmol/L)	6.3 ± 1.2	5.4 ± 0.9	0.01
Adenosine (μmol/L)	0.28 ± 0.16	0.39 ± 0.19	0.05
Cysteine (μmol/L)	210 ± 18.5	163 ± 14.6	0.001
Total glutathione (μmol/L)	7.9 ± 1.8	4.1 ± 0.5	0.001
Oxidized Glutathione (nmol/L)	0.3 ± 0.1	0.55 ± 0.2	0.001
GSH/GSSG Ratio	25.5 ± 8.9	8.6 ± 3.5	0.001

Table 2: Metabolites in the methionine cycle and transsulfuration pathway are abnormal in autism (data from Dr. Jill James).

The 20% lower levels of cysteine and 54% lower levels of glutathione in autistic children will adversely affect their ability to detoxify and excrete heavy metals and thimerosal. These two compounds directly bind inorganic and organic mercury and help direct them to the kidneys for excretion. As a result, these toxic materials will reach a higher free concentration in the bloodstream of autistic children, will have an increased potential for transfer to tissue compartments such as the brain, and will remain in the body for a significantly longer period of time, as compared to their counterparts who have normal levels of cysteine and glutathione. These differences begin to define the subpopulation of children who are more vulnerable to thimerosal and heavy metal exposure.

Earlier metabolic and genetic studies provide clues to the cause of the increased adenosine level in autism. Page and co-workers found 8 to10-fold higher activity of the enzyme that makes adenosine (5'-nucleotidase) in subgroup of children (13), while Stubbs and co-workers found that the enzyme that degrades adenosine (adenosine deaminase) has lower activity in autistic subjects (14). Genetic studies have also shown that a polymorphism in the adenosine deaminase that weakens the enzyme is more common among autistic subjects (15). Impairment of adenosine deaminase, may result from dysfunctional interactions with its binding partner, enzyme dipeptidyl peptidase IV. As illustrated in Fig. 10, these metabolic defects can combine with thimerosal exposure and other genetic risk factors to inhibit methylation and cause autism.

There is recent evidence that polymorphisms in genes for methionine synthase and closely-related enzymes are another source of risk for autism. For example, there are two well-characterized disabling polymorphisms in the methylenetetrahydrofolate

reductase (MTHFR) gene, the enzyme that makes methylfolate available to methionine synthase, and these polymorphisms are more common in autism (16). MTHFR polymorphisms reduce methylfolate levels, which slows the methylation of Cob(I) and increases the probability that it will oxidize to Cob (II). As a consequence, MTHFR polymorphisms increase methylcobalamin demand for the three-domain form of methionine synthase. A disabling polymorphism in methionine synthase, in a location that can affect the proportion of three- *vs.* four-domain enzyme forms, is reported to be six-fold more prevalent in autistic children (17). Finally, a polymorphism in the enzyme methionine synthase reductase, which assists in the rescue of cobalamin, may also be more frequent in autism (18). While other polymorphisms remain to be discovered, these examples serve as examples of genetic risks that characterize autistic children, making them more sensitive to the toxic effect of thimerosal and more prone to develop autism.

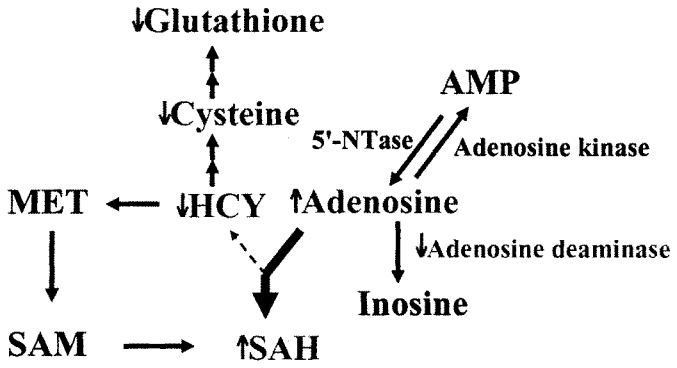

Figure 10: Decreased activity of adenosine deaminase or increased activity of 5'-nucleotidase (5'-NTase) can increase adenosine levels, resulting in lower levels of HCY, cysteine and glutathione.

6. Methylation-related Treatments for Autism

If impaired methylation is important in causing autism, metabolic interventions that augment methylation should be effective treatments. More specifically, if thimerosal's inhibition of methylcobalamin synthesis is important in causing autism, then the administration of methylcobalamin should significantly improve autism. Indeed, this has proved to be the case. As first reported by Dr. James Neubrander (19), injections of methylcobalamin, given once every three days, has brought about significant improvement in approximately 80% of children with autism. While the degree of improvement varies, a significant number of children have improved to the point that they are no longer considered to be "on the autism spectrum". Areas of particular improvement include language, attention and social skills, which are hallmark symptoms of autism. Within the next few months, the M.I.N.D. Institute at the University of California at Davis School of Medicine is slated to carry out a controlled study of methylcobalamin effectiveness in autism.

Other methylation-promoting treatments are also proving helpful in autism. In the metabolic study carried out by Dr. Jill James and colleagues (12), autistic subjects were treated with folinic acid (leucovorin), a folic acid derivative that augments levels of 5-methylTHF, along with betaine (trimethylglycine), which feeds methyl groups to the folate pathway. These two agents normalized most of the abnormal metabolites listed in Table 2, and this was accompanied by clinical improvement in autism symptoms. Subsequent addition of methylcobalamin to this regimen brought about further improvement.

While encouraging, these metabolic interventions do not help many autistic children, and there is a need for additional treatment approaches. Moreover, improving methylation capacity is only one component of the multi-dimensional approach to treating autism. Other elements such as a gluten-free/casein-free diet, chelation of heavy metals and intensive behavioral therapy are also important. Additional metabolic interventions, particularly interventions directed at normalizing adenosine metabolism may prove fruitful. Clearly further research is needed, building upon the framework of knowledge about how genetic and environmental factors can synergize to cause autism.

7. Conclusions

Autism is a neurological disorder caused by dysfunctional metabolic control over methylation reactions, and thimerosal appears to be a precipitating causative factor in many cases. The methionione cycle and the trans-sulfuration pathway leading to cysteine and glutathione synthesis are abnormal in autism. Genetic polymorphisms, present in only a small subpopulation, represent risk factors for autism. As illustrated in Fig. 11, some of these genetic factors impair detoxification and clearance of heavy metals, including thimerosal, and also impair the capacity for methylation. Delayed clearance of thimerosal further impairs methylation, including both DNA methylation and dopamine-stimulated phospholipid methylation, adversely affecting growth factor-directed development and the capacity for attention, respectively. Autism can be treated, and some of the most effective treatments, such as methylcobalamin, act by improving methylation. This encouraging therapeutic development reinforces the conclusion that thimerosal does indeed cause autism, and it does this by interfering with methylcobalamin synthesis. This

molecular understanding should lead to new and improved treatments for autism and should provide a scientifically sound basis for the removal of thimerosal from all vaccines.

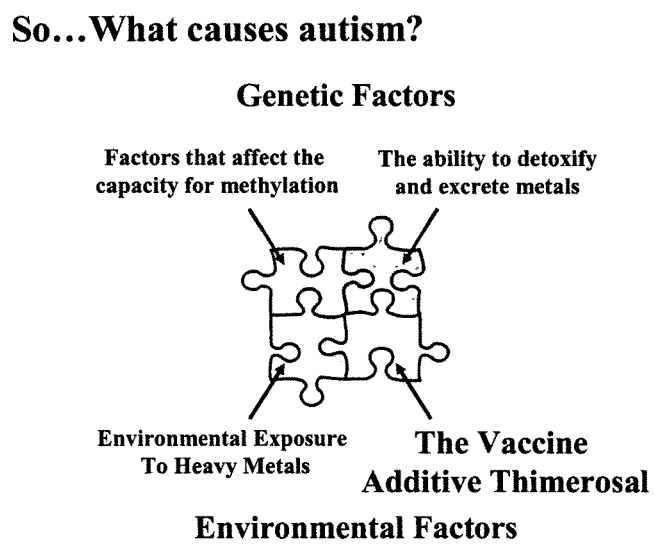

Figure 11: Genetic and environmental factors combine to cause autism.

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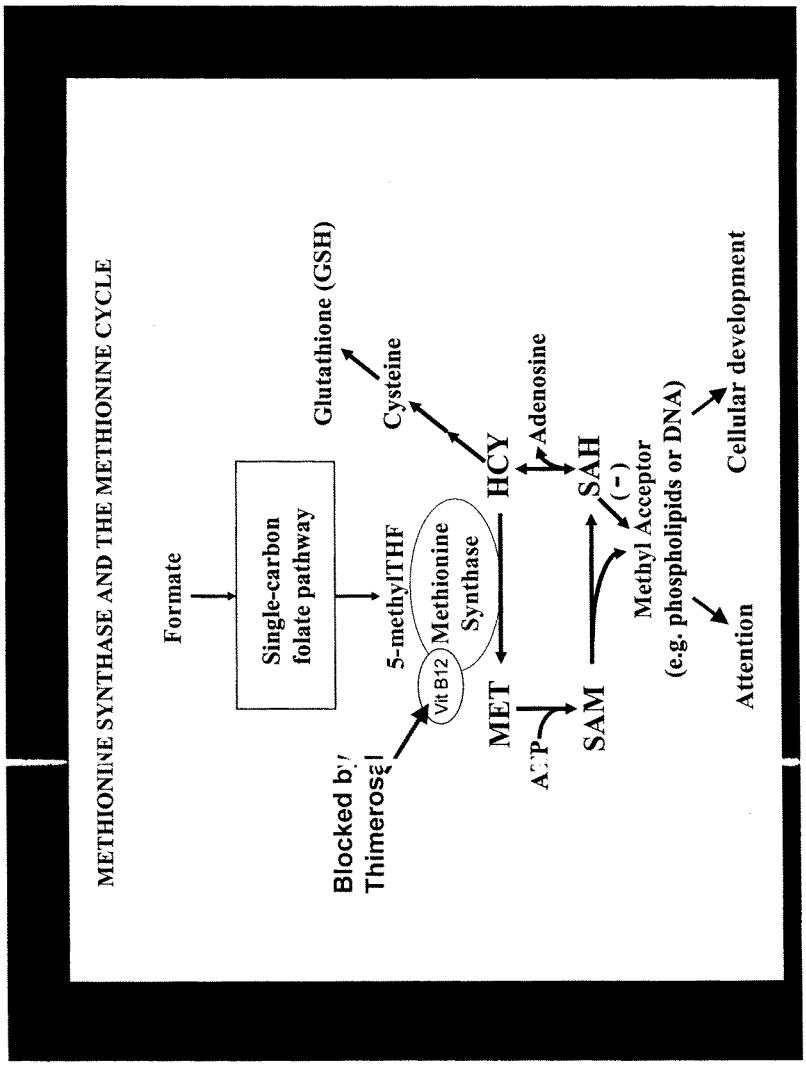
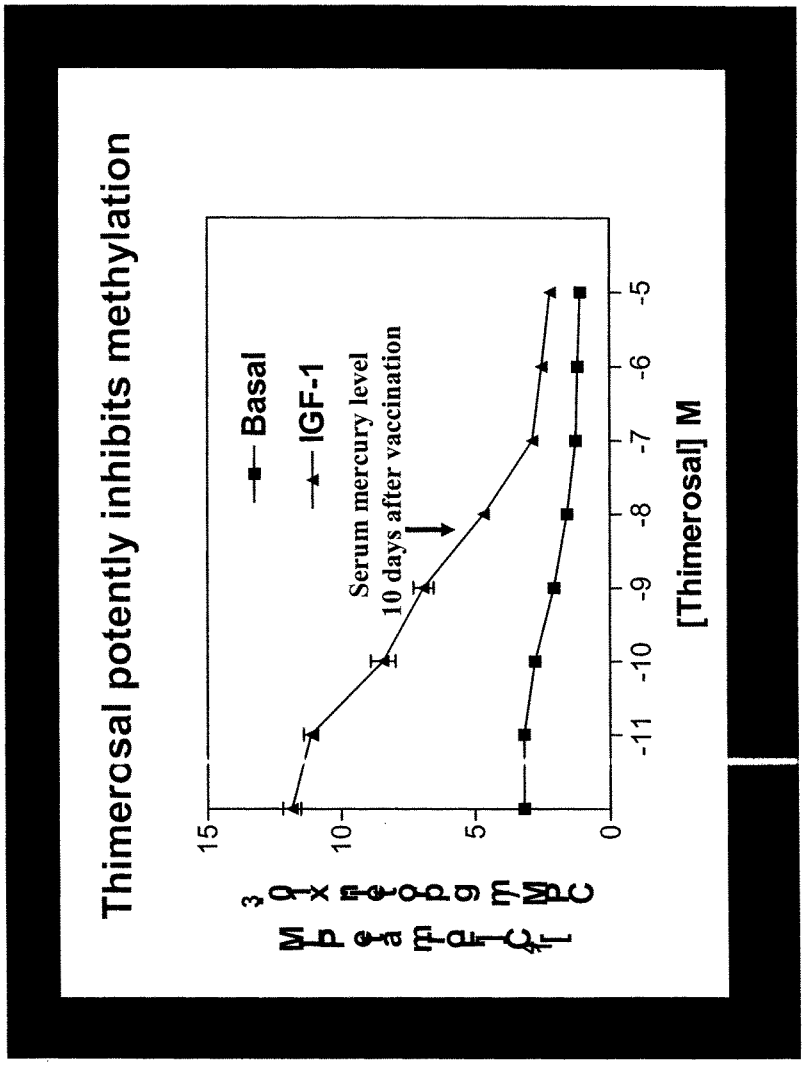
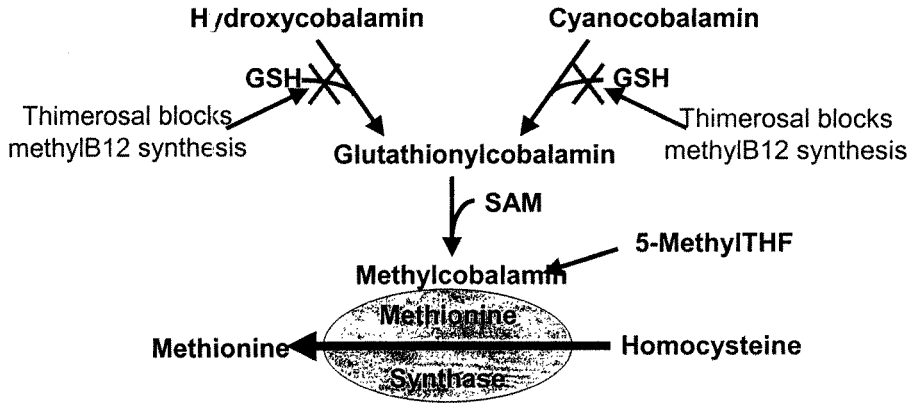
Molecular Aspects of Thimerosal-induced Autism

Richard C. Deth, Ph.D.
Professor of Pharmacology
Northeastern University
Boston, Massachusetts


METHIONINE SYNTHASE AND THE METHIONINE CYCLE
Formate
Single-carbon folate pathway
Glutathione (GSH)
Cysteine
5-methylTHF
Vit B12
Methionine Synthase
HCY
Adenosine
SAH
(-)
Methyl Acceptor
(e.g. phospholipids or DNA)
Cellular development
Blocked by
Thimerosal
MET
ATP
SAM
Attention


Thimerosal potently inhibits methylation
Basal
IGF-1
Serum mercury level
10 days after vaccination
15
10
5
0
-11
-10
-9
-8
-7
-6
-5
[Thimerosal] M

Thimerosal blocks the synthesis of active MethylB12



Autistic children have metabolic abnormalities involving the methionine cycle and the natural antioxidant glutathione

Data from Dr. Jill James

	Control Children n=33	Autistic Children n=20	p value
Methionine (μmol/L)	30.6 ± 6.5	19.3 ± 9.7	0.001
SAM (nmol/L)	90.0 ± 16.2	75.8 ± 16.2	0.01
SAH (nmol/L)	20.1 ± 4.3	26.1 ± 5.4	0.001
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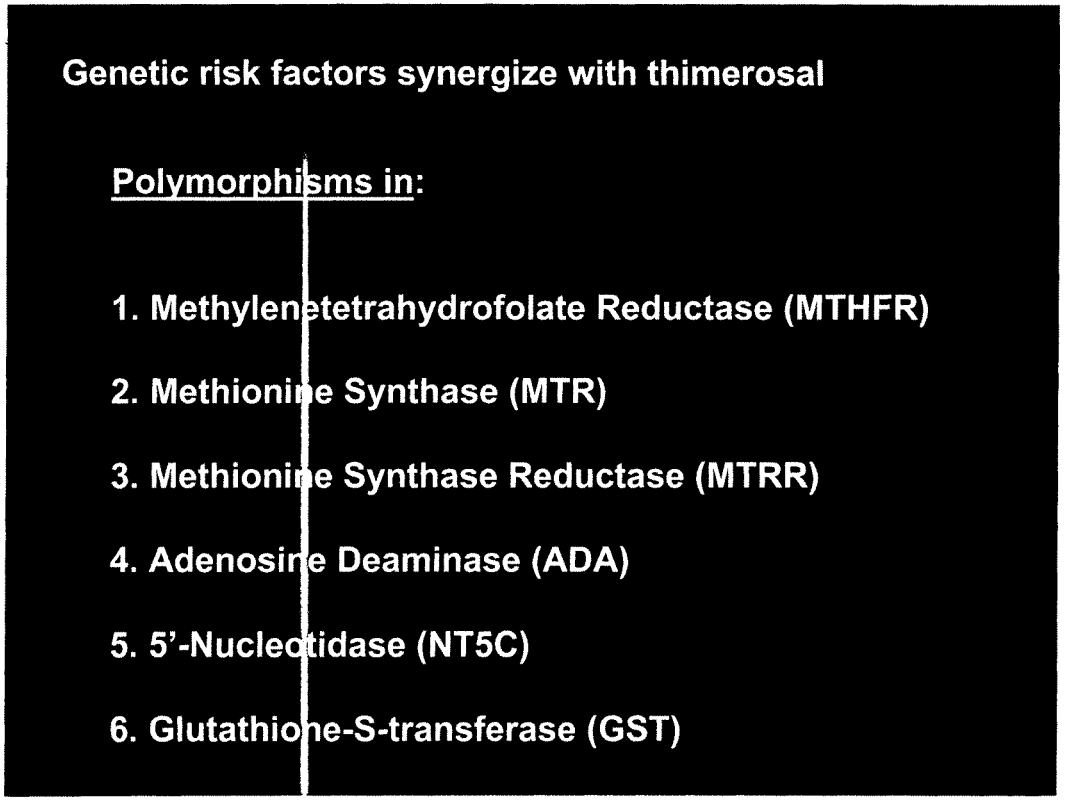
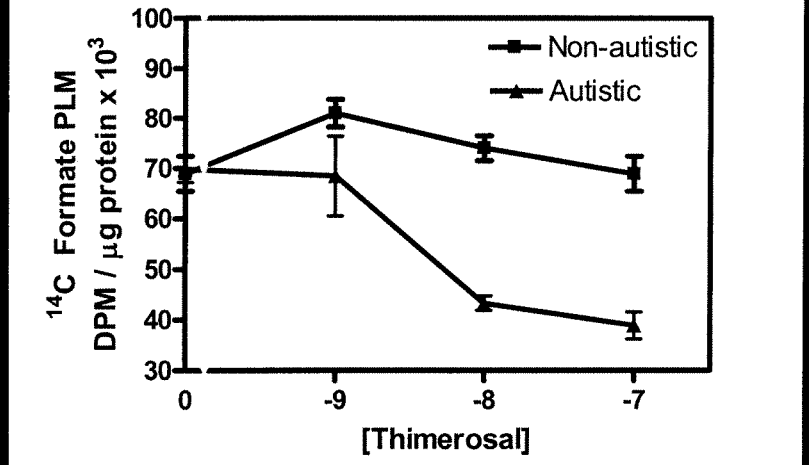
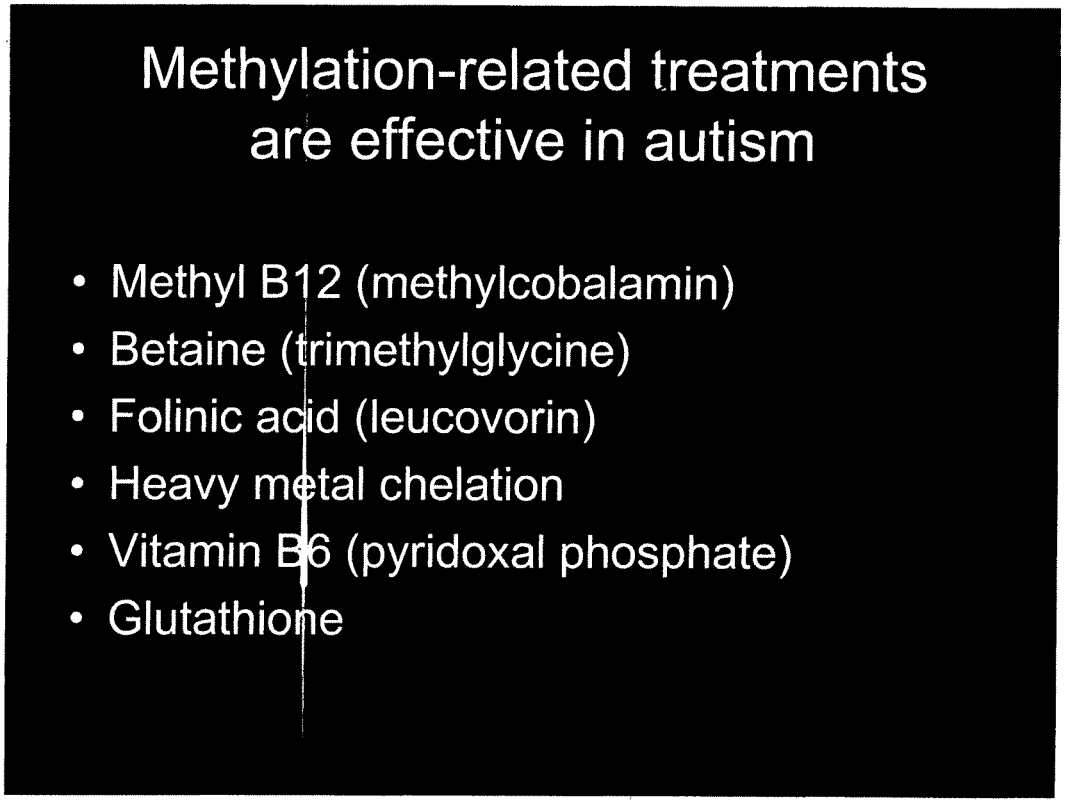
Adenosine (μmol/L)	0.28 ± 0.16	0.39 ± 0.19	0.05
Cysteine (μmol/L)	210 ± 18.5	163 ± 14.6	0.001
Total glutathione (μmol/L)	7.9 ± 1.8	4.1 ± 0.5	0.001
Oxidized Glutathione (nmol/L)	0.3 ± 0.1	0.55 ± 0.2	0.001
GSH/GSSG Ratio	25.5 ± 8.9	8.6 ± 3.5	0.001


Genetic risk factors synergize with thimerosal
Polymorphisms in:
1. Methylenetetrahydrofolate Reductase (MTHFR)
2. Methionine Synthase (MTR)
3. Methionine Synthase Reductase (MTRR)
4. Adenosine Deaminase (ADA)
5. 5'-Nucleotidase (NT5C)
6. Glutathione-S-transferase (GST)

Lymphoblasts from autistic children show greater sensitivity to thimerosal than cells from non-autistic, same-sex siblings



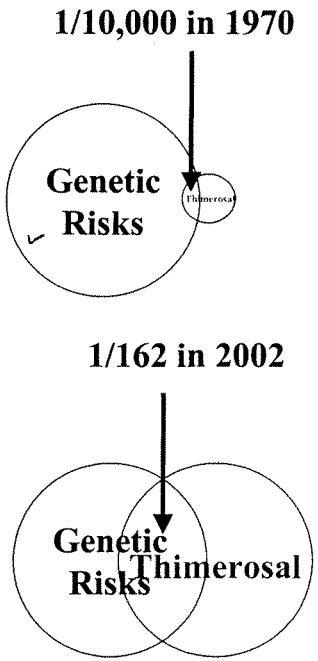

Methylation-related treatments are effective in autism
• Methyl B12 (methylcobalamin)
• Betaine (trimethylglycine)
• Folinic acid (leucovorin)
• Heavy metal chelation
• Vitamin B6 (pyridoxal phosphate)
• Glutathione

Conclusions

- Thimerosal causes autism by inhibiting folate-dependent methylation.
- Thimerosal inhibits methylation by blocking the conversion of vitamin B12 to its active form, methylcobalamin.
- Genetic polymorphisms related to methylation pathways increase thimerosal toxicity.
- In many cases autism can be improved by metabolic treatments that increase methylation.

What caused the the Autism Epidemic?

Increased exposure to heavy metals (i.e. from increased thimerosal in vaccines) results in a higher risk from genetic factors.

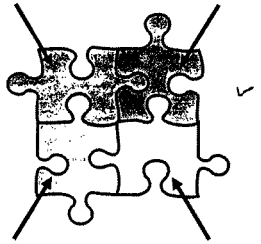


So…What causes autism?

Genetic Factors

Factors that affect the capacity for methylation

The ability to detoxify and excrete metals



Environmental Exposure To Heavy Metals

The Vaccine Additive Thimerosal

Environmental Factors

Mr. BURTON. I want to ask you a question right now, but this is pretty conclusive scientific evidence, in your opinion?

Mr. DETH. The combination of both molecular studies from our lab and the results of blood measurements in autistic children and the genetic profiles of autistic children showing the presence of genetic risk factors in the same area, and the fact that treatments directed toward this same area improved clinically autistic children, in some cases making them non-autistic, seems to me, in my personal and professional opinion, to be overwhelming evidence that this is the area from which autism arises, and that thimerosal's insult to this area has produced the dramatic increase in autism that we've observed.

Mr. BURTON. Thank you. I will have some more questions for you.

Dr. Just.

STATEMENT OF MARCEL JUST, PH.D., PROFESSOR OF PSYCHOLOGY, D.O. HEBB CHAIR, CARNEGIE MELLON UNIVERSITY

Mr. JUST. Mr. Chairman, members of the subcommittee, it is such a pleasure for me, Mr. Chairman and members of the subcommittee, to be here today, because I think in trying to get at the causes of autism, you have to know what the end state is, to understand the nature of autism. It is after all something, a disease of the brain.

And we, my colleagues and I at Carnegie Mellon, other universities, have with considerable Federal funding through NICHD and the centers, the collaborative programs for excellence in autism have been working on this for 5, 6, 7 years. I think we have something new to tell you today.

Let me show you, I want to start a little bit and tell you that brain imaging science that has just taken off in the past 10 years has given us a new view of how the brain works. One of the important things bears on autism. You see pictures in Newsweek and Time of some lit-up brain area. I have some of those, too. But really, that doesn't tell the right story.

The story is that any kind of thinking, your listening to my sentences right now, entails the use of a group of areas, a team of areas in the brain working together, 10, 12, depending how you count, say 5 to 20 areas of the brain, work together. It's a team effort. That wasn't very clear, but now with brain science, we do know that is absolutely the case.

I want to say something about autism. As you know, it's very enigmatic. Here you have people who are sort of nice, decent and smart people and yet you know that their thinking is somewhat disordered. Many of us have seen the movie Rain Man, many people have met people with autism. And it's hard to put it together.

There's an enigma. The fact that you know that there's an overall kind of not adequately coping with the world and yet at the same time being good at some specific tasks, some narrowly focused tasks. We wanted to look at this in brain imaging, and let me tell you a sort of a microcosm, a little micro-world where this is true, and it's in the area of language.

Do you know that people, high functioning people with autism do pretty well at spelling bees? They can spell words better than average. They can read words better than average. At the same time, they have more difficulty in understanding a complex sentence. How do you put that together? They're good at the pieces and not good at the puzzle.

That's what we went after, and we did a brain imaging study that asked people, control participants and mainly adult people, high functioning people, normal i.q. range. We gave them sentences like the farmer was followed by the parent who was following, they're lying in an MRI scanner, they're looking at a little screen, they're reading on a little screen and they press buttons saying whether it's the farmer or the parent.

And while they're doing this, through the magic of MRI, and particularly FMRI, we measure where the blood, where the oxygen in their brain is flowing. We measure it on a second by second basis, so we get a movie of the brain activity while they're doing the sentence comprehension.

Here's the result. And it's so interesting, I don't want to get too technical, but I have pictures of, I see my pointer isn't showing up. There are two areas lit up there. The one to the left is Broca's area, it's in the front. It kind of does sentence processing. It's a gross oversimplification, but it does sentence processing. And the one to the right behind is Wernicke's area. And another oversimplification is that it does word processing.

If you look at the brain activation in the autistic population, that's a group image up above, there's relatively more activation in the area on the right, Wernicke's, in the word area, and relatively less in the sentence area, compared to the control subjects down below. For these sentences, the people with autism can work their way through it by focusing on the individual words, working really hard with the individual words.

But the way they differ from the control subjects is the control subjects are putting the pieces together of the individual words to make up the sentence in Broca's area, by looking at the grammatical relations between the words, the syntactic relations.

Now, I want to make a very important point here. I don't think that Broca's area is broken, I don't think it's at fault. I don't want to point the finger at Broca's area. I don't think autism lives in one place in the brain, certainly not in Broca's area. I think it's a neural systems disorder that's caused by a lack of adequate communication among areas. How could the area that puts the pieces together put the pieces together if it doesn't get adequate information about the pieces?

So that's just the first part of the story, the integrating area works less well than the individual pieces area. So that's one piece of the puzzle.

Here's another one. As we measure the activity in these various areas, it's not a photograph, it's a movie. We measure the activity every few seconds. We can see, we measure the activity in one area, the activity in another area, we can see how well it's synchronized. Are the two areas marching to the same drum?

The finding is that the degree of synchronization is lower in the people with autism. And you know, we've done this in lots of stud-

ies, it's a robust finding. I illustrated here in this graph, the upper graph is from a person who has autism and the two lines show the level of activity in the two brain areas. And the two areas you can kind of see track each other decently.

But if you look at the person without autism down below, they track each other much better. So there's lower synchronization, just the activity level is marching to the same drum in the case of people without autism.

We measured one of the main white matter tracks in these people. The corpus callosum is the main cable, so to speak, connecting the left and the right hemisphere. And in general, it was smaller in the people with autism. So think about it, the cable that provides the communication is smaller. That's got to impact bandwidth, how much information you can put through it per unit time. That's the third piece of the puzzle.

Differences in white matter. Now, I should say, we're not the leading laboratory in measurement of white matter. But there are wonderful findings, I want to mention Dr. Martha Herbert, who had a paper on this recently that precisely measured white matter throughout the brain of people with autism, finding reliable and systematic differences. But we focused here on the corpus callosum.

And one more, here's the fourth piece of the puzzle, and I think this for me nails it. The size of the relevant piece of the corpus callosum, it's called the posterior midbody, but don't worry about that, the size, the diameter of that area predicted how well we're synchronized, the two brain regions that cable connected. That's the scatter plot here.

The smaller the posterior midbody was in these people with autism, the worse was their synchronization. If you look at this plot, I don't have it here for the people without autism, there's no relation, because the corpus callosum doesn't constrain, doesn't limit how that synchronization goes.

Mr. BURTON. The one thing that we were interested in is the mercury impact on these areas. You haven't mentioned anything about that. Is that a part of this?

Mr. JUST. I'm afraid not, Chairman Burton. This is an end stage, if you're going to look for causes, you need to have a precise description of the causes. I believe that this is a large step forward in improving the precision of the description of autism, of what it is, how it affects people.

Mr. BURTON. OK, that's fine. We'll get back to that in questions. We'll maybe ask you questions about how these things correlate with one another.

[The prepared statement of Mr. Just follows:]

Written Testimony of

Marcel Just, Ph.D.,

Professor of Psychology, D.O. Hebb Chair,

Carnegie Mellon University

House Government Reform Subcommittee on Human Rights & Wellness

September 8, 2004

"Thank you for this opportunity to tell you about significant advances in understanding the neural basis of this enigmatic and tragic disorder called autism. I come before you with pride that an arm of my government is motivated by compassion to seek the advances of medical science in understanding this disorder. I am going to describe some of the new findings from my research center and others that together paint a different picture of autism than the one we had even 10 years ago. With the help of federal and private funding, significant new inroads have been made.

This statement is written in language that I hope every educated layman can understand. It includes a little bit of technical information, but no more than the information we have about how our cars or our computers work. We need to understand how the brain works, and what it is that is disordered in autism. Armed with this knowledge, we can see how to approach the problem of autism right now, in terms of new types of therapies, and we can see how to target the next iteration of research so that we can approach a cure.

I am going to tell you my punch line right now. Autism doesn't live in one particular part of the brain. Rather, it is a neural systems disorder. The disorder is the result of underdevelopment of the connectivity among different brain areas. In modern computer terms, the problem isn't with this microchip or that microchip, but with the network connectivity among processing centers or chips.

This oversimplified metaphor goes a long way to explain the basic enigma of autism. The metaphor explains how it is possible that intelligent people with autism can have some well-developed skills, but can still be very unlike unaffected people in terms of their thinking and interpersonal abilities, and still have considerable difficulty living an independent life.

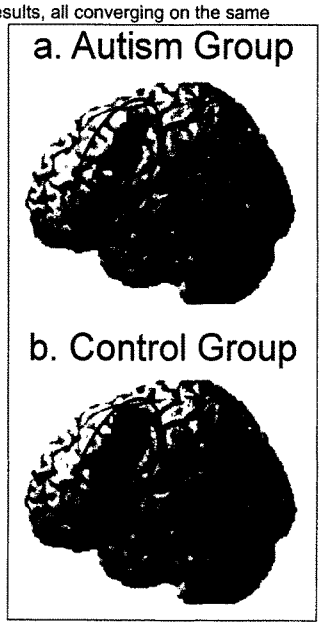
Here is a picture of the problem in microcosm. One of the areas in which people with autism (at least those with IQ's in the normal range) do as well as and sometimes better than controls is in word reading. The perception of single words is enhanced. The capacity to pronounce them, spell them, define them is superior to other children of their age and IQ. You may find children with autism or Asperger's syndrome competing successfully in spelling bees. Yet at the same time, if you ask people with autism to follow some complicated instructions e.g. comprehend a complex sentence, they do worse than their control group. So the enigma is, how can people with autism be better than average in word reading, but worse than average at understanding complicated sentences?

That last question was one that we were able to answer with a brain imaging study. My colleagues and I, particularly Dr. Nancy Minshew, tested a group of 17 adults with autism who had IQ's in the normal range, and compared their brain activity with a group

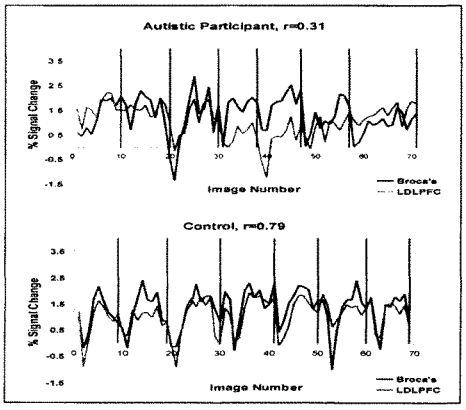
of matched control subjects. The task we asked them to perform was to read a sentence like "The farmer was followed by the parent" and then answer a question like "Who was doing the following, the farmer or the parent?" They did this while they were lying in an MRI scanner and reading the sentence on a projector screen in the scanner. We measured their brain activity (using functional MRI) literally measuring the oxygen concentration in every part of their brain every 3 seconds. By seeing where the oxygen was going, we can tell which parts of the brain are at work and how hard they are working.

There were 4 absolutely fascinating and unexpected results, all converging on the same new theory.

First, the autism group had less activation in Broca's area (a sentence integration area, in the leftmost oval) than the control group and more in Wernicke's area (a word processing area, in the rightmost oval). The people with autism are doing less integrative thinking and are focusing more on the words in isolation (Just et al., 2004).

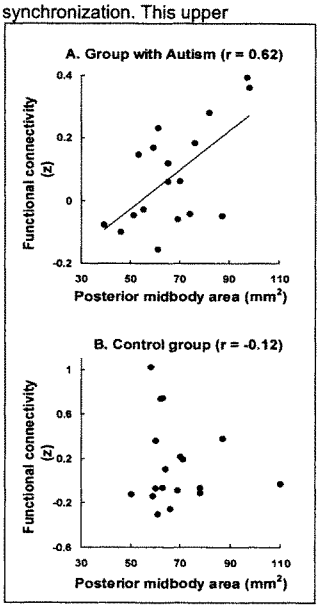


Second, the brain activity was less synchronized between various brain areas in the adults with autism. For the control subjects, the activity in one brain area went up and down at the same time as in another brain area. The areas were more synchronized, or better coordinated. The figure below shows that the red and green lines (activity levels in two brain areas) track each other considerably less well in the person with autism as indicated by the r value.



Third, one of the major fiber tracts in the brain connecting the left and right side of the brain was slightly smaller in the people with autism. This fiber tract is called the corpus callosum. It doesn't do any processing itself but it does connect the different brain areas of the brain that do the processing. Martha Herbert and her colleagues (2004) have reported similar abnormalities of the cabling (white matter) in autism. It is the white matter of the brain that is thought to cause the brain in autism to grow too large in early childhood at the time of onset of symptoms.

Fourth, the size of the corpus callosum was correlated with how synchronized the brain areas in the left and right hemisphere were. The diameter of this cable -the corpus callosum - was correlated with the amount of synchronization of the two brain areas that it connected. The smaller it was, the lower the degree of synchronization. This upper scatterplot shows the correlation, where functional connectivity is the measure of synchronization. The lower scatterplot shows that in the control group, which had a larger corpus callosum, there was no relation between the size of the cable portion and the amount of synchronization.



All four of the above findings point to the same conclusion: underconnectivity of brain areas in autism.

There is additional evidence which I have not shown you to support this underconnectivity conclusion. For example, the findings have been obtained not just in a language task, but also in a problem-solving task, and a social task, thus occurring in all three of the main symptom domains of autism The theory also predicts that information transfer between brain regions will be reduced and a study requiring formation of a visual image from a verbal description has demonstrated this to prediction to be true. Also, the theory predicts particular difficulty in multitasking in autism, even in cases where each of the two tasks can be performed perfectly well by itself, but is much more poorly performed than by controls in a multitasking situation (Garcia-Villamisar et al., 2002). The reason that difficulties are greater in multitasking is that executing two concurrent tasks requires an especially large amount of inter-area coordination, and underconnectivity makes such a multi-tasking much more challenging.

The new findings aren't just scientific esoterica to be buried in a journal. They provide the basis for developing new therapies that attempt to minimize or overcome the problems of underconnectivity. The new results also help set the sights for the next round of research, to find out why brain connections aren't developing normally, and what genetic or pharmacological interventions might help remediate this problem.

I came here to show you the scientific ledgers from our laboratories, not the financial ledgers. But at the end of the day, both ledgers have to balance. The current level of federal funding has enabled us to come this far, and now is the time to accelerate, not to slow down. We are now more sure than ever that we are on the right road, and our target is clearer. Federally supported research centers like the NICHD Collaborative Programs of Excellence in Autism (CPEA's) as well as others are leading the charge. Your continued and increasing support is essential to make this vital journey reach its destination, to use the power of science and medicine in the service of innocent victims of autism and their families. We also wish to express our tremendous appreciation of the individuals who have participated in our studies. We wish to encourage others to do so as the pace of progress is only as fast as the numbers of individuals who volunteer. The importance of normal controls cannot be under-emphasized.

Thank you for your interest in this area of medical research science. With your help, we can continue to make critical new advances in the field of autism research that will change peoples' lives."

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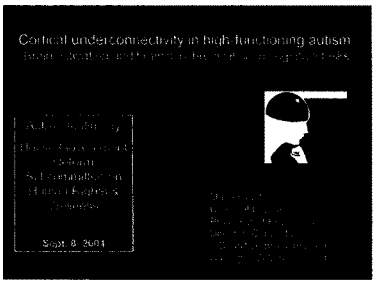
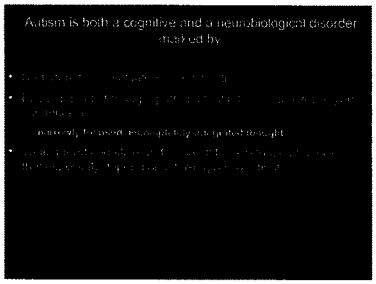
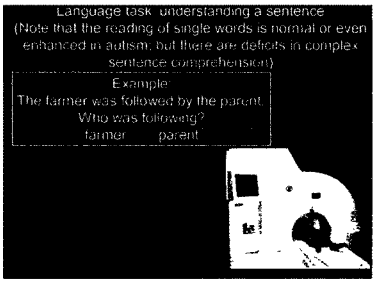
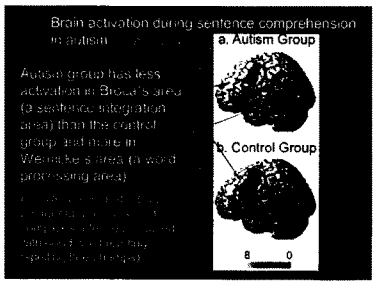
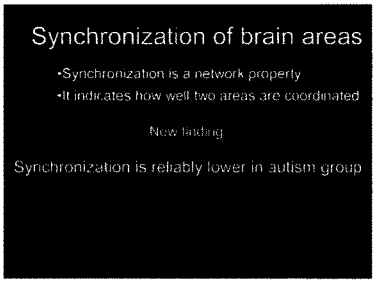
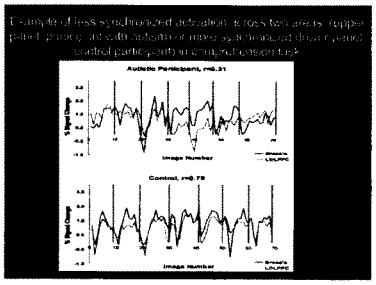

Cortical underconnectivity in high-functioning autism
Sept. 8, 2004

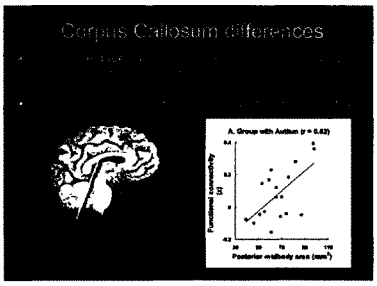

Autism is both a cognitive and a neurobiological disorder
characterized by

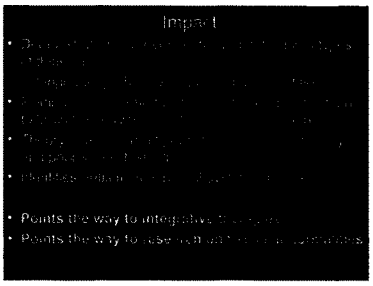

Language task: understanding a sentence
(Note that the reading of single words is normal or even enhanced in autism, but there are deficits in complex sentence comprehension)
Example:
The farmer was followed by the parent.
Who was following?
farmer parent


Brain activation during sentence comprehension in autism
a. Autism Group
b. Control Group
8 0


Synchronization of brain areas
•Synchronization is a network property
•It indicates how well two areas are coordinated
New finding
Synchronization is reliably lower in autism group


Autistic Participant, req.31
Control, req.79
Image Number


Corpus Callosum differences
A. Group with Autism (r = 0.62)
Functional connectivity
SD
0.4
0.2
-0.2
Posterior midbody area (mm²)


Impact
Points the way to integrative
Points the way to

Mr. BURTON. OK. Ms. Redwood.

STATEMENT OF LYN REDWOOD, R.N., MSN, PRESIDENT, COALITION FOR SAFEMINDS

Ms. REDWOOD. Good morning, Chairman Burton and members of the subcommittee. My name is Lyn Redwood. As president of the Coalition for SafeMinds and parent of a child with mercury-induced autism, I want to thank you on behalf of the entire autism community for holding this important hearing today.

Given the prescribed time to take my comments, I am providing a copy of the newly released report from SafeMinds entitled A Brief Analysis of Recent Efforts in Mercury Medical Induced Neurological and Autism Spectrum Disorder, and ask that it along with my full written testimony be entered into the hearing record.

Since the scientists present here will be testifying regarding their research telling the connection between thimerosal and autism, I have chosen to limit my oral testimony to the response of our Federal agencies to this issue.

How I came to this discussion, I'm here today because of my son Will. These pictures show you a healthy, alert, happy, non-autistic boy. This is my son after he received toxic levels of mercury, 125 times his allowable EPA exposures. He was just a shell of his former self. I share this personal information with you to bring to you the reality of Government policy. What we discuss here today is not just a theoretical risk, but actual injury.

It has been 5 years since the Public Health Service and the American Academy of Pediatrics first announced that thimerosal should be removed from vaccines. And at that time, taking the appropriate position of caution, they announced to the public and practitioners, "Because of any potential risk or concern the Public Health Service, the American Academy of Pediatrics and vaccine manufacturers agree that thimerosal-containing vaccines should be removed as soon as possible.

This next slide, on the left is a picture of a boy from the 1930's who suffered from acrodynia, which was a form of mercury toxicity resulting from exposure to mercury in teething powders. On the right is my son after developing mercury toxicity.

In July 2000, when SafeMinds presented to the Government Reform Committee a paper, Autism: A Novel Form of Mercury Poisoning, publishing the evidence pointing to the synonymous nature of the symptoms of mercury poisoning and autism spectrum disorders, we could not have imagined that in 2004, thimerosal would still be in vaccines and that the Government agencies tasked with protecting the public would have failed to take aggressive action to get the mercury out. We could not have imagined that the Department of Health and Human Services would instead have focused their energies on avoiding the truth that's before them, and in doing so, undercut the public's trust in vaccine programs, and continuing to put babies at risk.

The first in a series of regulatory failures of our Government agencies belongs to the Food and Drug Administration for failing to remain open minded and objective about the possibility that vaccines might at times be harmful, and requiring valid scientific evidence from manufacturers to prove safety of vaccines, their pre-

servatives and adjutants. Over the course of 70 years since thimerosal was first introduced into the marketplace, FDA has repeatedly failed to ask tough questions and require proof of safety, while allowing its increased use in vaccines.

But worse than this initial series of failures is that which has occurred since the July 1999 announcement. The Coalition for SafeMinds asked the FDA to immediately conduct a recall and protect every child from potential mercury injury. The FDA denied this request as they denied your request, Chairman Burton, citing their fear that industry would sue because they had "no proof of harm."

Since then, two citizens' petitions have also been submitted to the FDA asking for recall and ban on thimerosal-containing vaccines, one by the National Vaccine Information Center in 2002 and just recently another by the Coalition for Mercury-Free Drugs in July 2004. These petitions seek to make the FDA enforce its own regulations that unless a component of a drug has been proven safe it must be removed. Neither of these petitions have been responded to or acted upon at this time.

I and many of my medical colleagues remain astonished that we even have to ask the FDA to stop allowing mercury to be injected into babies. We've trusted that the FDA was doing its job and assuring the safety of all drugs and biologics it regulates, and that trust has been proven under-served in this instance.

CDC failures are even more egregious. At every turn when the CDC could have alerted the public and taken a strong stand against the use of thimerosal, they instead have promoted flawed epidemiological studies as proof that no evidence of harm has existed. If the uninformed public takes the statements on the CDC Web site at face value, they could conclude that rigorous evaluations have been conducted and that no risks are associated with the use of thimerosal in vaccines. Nothing could be further from the truth.

In July 2000, when you had the CDC before you, your committee, they made no mention of their own research looking at the link between thimerosal and autism. SafeMinds obtained relevant documentation through a Freedom of Information Act request which showed that by December 1999 the CDC knew thimerosal could be linked to the increased incidence of neurodevelopmental disorders.

Using taxpayer resources and ready access to the vaccine safety data link sets, CDC researcher Dr. Tom Verstraeten and his team looked at the medical records of children in a number of HMOs to see if there was any truth to the thimerosal autism hypothesis. Their results were so striking and deserving that they would next call for a private meeting away from the CDC complex and away from the public eye to discuss. This is the now infamous Simpsonwood meeting where Dr. Verstraeten presented his findings to a closed group of CDC and HHS officials and selected outside experts, many of whom were academic scientists with close ties to vaccine manufacturers.

The Simpsonwood meeting, ostensibly designed to be a careful review of the CDC analysis on the impact of thimerosal-containing vaccines on child development instead became a vehicle for making numerous deliberate choices that took positive findings in a single

direction toward insignificance. Between February 2000 and November 2003, Dr. Verstraeten and his supervisors at the National Immunization Program produced four separate generations of an analysis designed to assess the impact of vaccine mercury exposure on neurodevelopmental disorders in children. With each generation, elevated and statistically significant risks were reduced or eliminated.

But before these four generations of study were produced, Verstraeten conducted an earlier analysis of these issue in November and December 1999. He never prepared a formal report of the work, but statistic tables obtained by SafeMinds in a FOIA request not previously analyzed demonstrate large and statistically significant mercury exposure effects that in many cases exceeded the findings of their later reports.

The results of the generation zero analysis are striking and more supportive of a causal relationship between vaccine mercury exposures and childhood developmental disorders, especially autism, than any other results reported later. The elevated risk of autism for the highest exposure level of mercury at 1 month of age ranged from 7.4 to 11.4 times the zero exposure level. This increased risk level corresponds to a tenfold increase in autism rates seen since vaccine mercury exposures increased starting in 1990.

It's also interesting to note than in August 1999, with increasing pressure for scientists and researchers to gain access to this data base, a CDC employee, Dr. Chen, went to a meeting in Europe and created an organization which he named the Brighton Collaboration. The mission is to facilitate the development, evaluation and dissemination of high quality information about safety of human vaccines.

Their aim is to develop globally accepted and implemented standardized case definitions of adverse events following immunization. While on the surface this may seem like a worthy cause, a number of legitimate concerns need to be fully addressed, including how CDC employees are gaining CDC funding for their outside activities. I have outlined some of these concerns in my written testimony and ask for your assistance in gaining full disclosure from CDC on these issues.

In 2001, the CDC contracted with the Institute of Medicine to create an immunization safety review committee, in order to review the scientific evidence regarding a number of vaccine injury hypotheses, including the correlation between thimerosal-containing vaccines and the onset of neurodevelopmental disorders, including autism. The IOM's first report on thimerosal was issued in October 2001, and concluded that the evidence was inadequate to either accept or reject this hypothesis.

But they went on to find the hypothesis biologically plausible and called for a clear and scientifically sound path for research necessary to find these answers. That path include epidemiology but it also called for animal models, clinical, case study and other relevant research in keeping with the tenets of good science. The committee went even further to recommend that infants, children and pregnant women not be exposed to thimerosal-containing vaccines, a recommendation that was not embraced by our Federal agencies.

On May 18th, the Institute of Medicine Immunization Safety Review Committee issued their final report, which found that the biological mechanisms presented to their committee, including thimerosal's ability to induce DNA damage and apoptosis in neurons, disrupt methionine synthase pathways, a model of autism induced with vaccine level exposure to thimerosal in an autoimmune mouse, elevated levels of mercury in children with autism after challenge with a chelating agent in comparison to controls, along with data that children with autism are not able to effectively excrete mercury were only theoretical at best. They concluded that the body of epidemiological evidence favors a rejection of a causal relationship between vaccine thimerosal exposure and autism.

A causal relationship between autism and vaccinations cannot be proved or rejected based solely on the evidence from population-based epidemiological studies. Epidemiological studies are by definition not designed to prove causality, they can only provide statistical associations. Therefore, the committee's conclusion that the body of epidemiological evidence favors rejection of a causal relationship has no scientific meaning.

The committee admits in their report that population-based studies would not be able to detect sub-populations that could be genetically more vulnerable to mercury at lower doses than normal. By their own admission, an untested plausible biological explanation for the causal association is the genetic susceptibility theory. Why was this not emphasized as a worthy hypothesis to explore?

Access to data is important, but access means nothing if you do not have the resources to conduct research. The very reason taxpayers support significant resources, $27 billion, to be provided by the National Institutes of Health, is to conduct research free of industry or other outside influence, to get timely answers to important health related questions. Since the mid 1980's, we've seen the epidemic increase in the rates of autism, yet NIH and other health agencies have been slow to respond. Autism research in 1977 was only $22 million. Although that's increased over the last few years, it remains woefully inadequate.

The NIH's efforts to conduct and fund studies evaluating thimerosal have been at time misdirected and continue to be inadequate given the severity and the potential risks associated with the discovery in 1999 that 8,000 children a day were being exposed to potentially dangerous levels of mercury. While the entire research portfolio on autism spectrum disorders remains inadequate, the investment on thimerosal research is even more minuscule.

In previous hearings, HHS staff testified to you that they had nominated thimerosal to the National Tox Program managed by the NIH's National Institute of Environmental Health Services. But after more than 3 years of waiting, thimerosal has yet to hit the radar screen of the National Tox Program. There are 31 chemicals with a project leader assigned and a study designed, but thimerosal is not among them.

So is there scientific evidence to support a parent's claim that receiving thimerosal-laden vaccines caused their children to become ill? Is there evidence to validate that the presence of mercury in the bodies of young children who also happen to be autistic is of

concern? To those who remain open minded, there is ample evidence to support these concerns. When NIH has failed to fund studies, the IOM asked for non-profit organizations, such as SafeMinds to fund or supplement research at some of our country's most respected academic institutes.

While the NIH spends less than $59 per autistic child on research, families are paying tens of thousands out of pocket for therapeutic care for their thimerosal injured children. They have been forced to devote energy and resources to raise money for research from art auctions, dinners, tee-shirt sales for 5 years because NIH and HHS have chosen not to make this a priority.

The Office of Special Counsel, an independent investigative and prosecutorial agency operates as a secure channel for disclosure of whistleblower complaints and abuse of authority. I only point this out to let you know right now the Office of Special Counsel is currently investigating the issues with thimerosal.

I know I've gone over time. I will cut through this real quickly and go to Cautious Hope for California.

Mr. BURTON. You're talking about the bill that's on Governor Schwarzenegger's desk?

Ms. REDWOOD. Yes, sir.

Mr. BURTON. Well, we'll all be pushing to try to make sure that he signs that. I've already got a call in to him.

If you could summarize, though.

Ms. REDWOOD. I am. I have just a quick few more notes. Although the reduction of thimerosal in medical products, including vaccines, has taken over 5 years to accomplish, we may be starting to see some of the effects of this policy decision. According to information released in July 2004 by the California State Department of Developmental Services, California has experienced the first ever 9 month sustained reduction in the numbers of professionally diagnosed new cases of full syndrome autism being added to California's developmental disability service system.

What makes this historic reduction in new cases of autism so important is that those children come from the birth cohort years of 1999 and 2000, which Dr. Egan mentioned earlier. These are the years when serious efforts began to substantially reduce the amount of mercury-containing thimerosal from vaccines.

Vaccine safety is an important public health issue. Concerns voiced by parents, physicians and the scientific community regarding vaccine safety must be addressed with thoughtful, complete and unbiased investigations. I showed you pictures earlier of my son Will. Unfortunately, his mercury-induced autism was not an isolated incident. Last April, Unlocking Autism brought photos of autistic children that spanned the length of three football fields on the Capitol grounds. I must ask how many children were thimerosal injured because the FDA and CDC chose not to act aggressively in 1999 and how many more are at risk because mercury continues to remain in vaccines and other medical products.

Thank you.

[The prepared statement of Ms. Redwood follows:]

Sensible Action For Ending Mercury-Induced Neurological Disorders

Testimony of

Lyn Redwood, RN, MSN
President
Coalition for SafeMinds

Before the Subcommittee on Human Rights and Wellness
Committee on Government Reform
U.S. House of Representatives

September 8, 2004

Hearing

"Truth Revealed: New Scientific Discoveries Regarding Mercury in Medicine and Autism"

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Introduction

Good morning Chairman Burton and Members of the Subcommittee. My name is Lyn Redwood. As President of the Coalition for SafeMinds, and the parent of an autistic child, I want to thank you on behalf of the entire thimerosal-induced autism community for holding this important hearing today.

Given the prescribed time to make my comments, I am providing a copy of a newly released report from SafeMinds entitled *"A Brief Analysis of Recent Efforts in Medical Mercury Induced Neurological and Autism Spectrum Disorders."* I ask that it be entered into the hearing record today.

It has been five years since the Public Health Service (PHS) and the American Academy of Pediatrics (AAP) first announced that thimerosal should be removed from vaccines. At that time, taking the appropriate position of caution, the PHS and AAP announced to the public and practitioners:

"...because any potential risk is of concern, the Public Health Service (PHS), the American Academy of Pediatrics (AAP), and vaccine manufacturers agree that thimerosal-containing vaccines should be removed as soon as possible."

In July 2000 when SafeMinds presented to the Government Reform Committee the paper, *Autism a Novel Form of Mercury Poisoning*, publishing the evidence pointing to the synonymous nature of the symptoms of mercury poisoning and autism spectrum disorders, we could not have imagined that in 2004 thimerosal would still be in vaccines and that the government agencies tasked with protecting the public would have failed to take aggressive action to get the mercury out and protect our nation's children. We could not have imagined that they would, instead, have focused their energies on avoiding or hiding the truth that is before them, and in doing so undercut the public's trust while continuing to put babies at risk for mercury injury.

Government and Regulatory Failures Abound

Food and Drug Administration

The first in a series of regulatory failures of our government agencies belongs to the Food and Drug Administration (FDA) for failing to remain open minded and objective about the possibility that vaccines might at times be harmful and requiring valid scientific evidence from manufacturers to prove safety of vaccines, their preservatives and adjuvants. Over the course of seventy years since Thimerosal was first introduced into the marketplace, FDA has repeatedly failed to ask the tough questions and to require proof of safety while allowing its increased use in vaccines. Federal regulations provide review procedures for biological products, including vaccines, and submission of animal safety data for the finished biological product. One must ask why Thimerosal, destined for childhood vaccines, was allowed to bypass toxicological testing, the bedrock of pharmaceutical development. FDA openly admits that original safety data submitted in the 1930's where Thimerosal was administered to adult rats, mice, dogs and guinea

pigs, no histopathology on the brain was reported. Only one study in humans was received where Thimerosal was used as an experimental agent to treat meningitis.

"The earliest published report of thimerosal use in humans was published in 1931 (Powell and Jamieson 1931). In this report, 22 individuals received 1% solution of thimerosal intravenously for unspecified therapeutic reasons. Subjects received up to 26 milligrams thimerosal/kg (1 milligram equals 1,000 micrograms) with no reported toxic effects, although 2 subjects demonstrated phlebitis or sloughing of skin after local infiltration. Of note, this study was not specifically designed to examine toxicity; 7 of 22 subjects were observed for only one day, the specific clinical assessments were not described, and no laboratory studies were reported."[1]

Although those who received this experimental treatment suffered high mortality and morbidity, these poor outcomes were attributed to the severity of the disease and not to Thimerosal. From these initial investigations Thimerosal was assumed "safe" by FDA and its use was "grandfathered" without further toxicity testing required.

In the early 1980's concerns regarding Thimerosal arose and an expert panel was convened by FDA to review its use in topical over the counter products. The panel reported in 1982 that Thimerosal was "toxic, caused cell damage, was not effective in killing bacteria or halting their replication" and that Thimerosal is "not generally recognized as being safe or effective"[2]. It was not until 16 years later in 1998 that the FDA issued the final rule that required Thimerosal to be removed from OTC products. FDA gave the industry 16 years to phase out thimerosal's presence in OTC Products. However, the FDA has not fully enforced this rule as thimerosal products can still be found on the shelves in some pharmacies.

Even with heightened awareness within FDA that the use of thimerosal was questionable, the Center for Biologic Evaluation and Research (CBER) at FDA appears to have been asleep at the switch. For two decades after thimerosal safety was called into question within the agency, CBER didn't look to ban its use, rather they encouraged its increase use. On their own website the FDA states the one human study used to gain FDA approval for Thimerosal had limitations.

But worse than this initial series of failures, is that which has occurred since the July 1999 announcement. The Coalition for SafeMinds asked the FDA to immediately conduct a recall and protect every child from the potential of mercury-injury. The FDA denied this request, as they denied yours Chairman Burton, citing their fear industry would sue because the FDA had no 'proof of harm'. Two additional citizen's petitions have been submitted to the FDA asking for a recall and ban of thimerosal-containing vaccines - one by the National Vaccine Information Center[3] in January 2002 and another by the Coalition for Mercury Free Medicine[4] in July 2004. Convinced that the FDA is abdicating its responsibility to protect our population from the neurotoxin mercury, still present in excess of EPA safety limits in vaccines and other drugs to which the unborn and newborn are routinely exposed without informed consent, the Coalition for Mercury-Free Drugs (CoMeD) filed FDA Citizen Petition 2004P-0349, seeking to make this

[1] http://www.fda.gov/cber/vaccine/thimerosal.htm#t1
[2] 1982 Vol 47, No. 2 Federal Register
[3] http://www.fda.gov/ohrms/dockets/CITPETS/02citpet.doc
[4] http://www.fda.gov/ohrms/dockets/dailys/04/aug04/080404/04p-0349-cp00001-01-vol1.pdf

agency enforce its own regulations that, unless a component of a drug has been proven safe, it must be removed.[5] This petition, which asserts this unwarranted and uninformed exposure to a known neurotoxin is a violation of the Constitutional Right of Bodily Integrity, is accompanied by 1000 pages of epidemiological and clinical research demonstrating a causal association between mercury exposure and neurodevelopmental disorders, including autism. Neither petition has been responded to or acted upon.

The truth is that even before the 1999 announcement, FDA had over the preceding decade received early warnings they chose to ignore. Between 1990 and 1998 the FDA received 47 adverse events reported through the Vaccine Adverse Events Reporting System (VAERS) regarding mercury or thimerosal. From 1998 to July 2000 another 15 reports were received. These 'red flags' were ignored.

Since 1990, FDA's CBER has funded 31 studies with its own scientists evaluating thimerosal, yet none of those studies appear to have been about toxicity, rather they have been studies to understand and enhance stability, analysis of total mercurial content, and other studies one conducts on materials whose use you want to promote. Resources they could have used to conduct the much needed pharmacokinetic studies, determining toxicity and maximum safe exposure levels, were not conducted (or have not been made available to the public if they have been done). Rather staff time and limited FDA research resources have done the work of industry in looking to make thimerosal more widely used.[6]

The FDA has failed the American public by ignoring its own data and the published data of numerous respected academic institutions showing that thimerosal is highly allergic to a significant portion of the population and that it does indeed harm the brain. Just a simple Medline search reveals hundreds of peer reviewed articles which document the toxicity of Thimerosal, including severe morbidity and mortality from high level exposure. They have repeatedly failed the public by putting the profits and preferences of industry above the safety of children.

I, and many of my medical colleagues, remain astonished that we even have to ask the FDA to stop allowing mercury to be injected into babies. We have trusted that the FDA was doing its job and assuring the safety of all of the drugs and biologics it regulates and that trust has been proven undeserved in this instance. Mercury in all of its forms is a known toxin. The unborn, the newborn, and the very young are particularly susceptible to brain injury from exposure, yet the FDA approved the use of Thimerosal to be administered in Rho-D immune globulin products injected into pregnant (and nursing) women with Rh-negative blood. They also approved the use of Hepatitis B vaccine with mercury to be given to babies within hours of birth. They approved DTaP, Hep B, Hib, Hep A, and the flu vaccine for use in infants and young children with the mercury-based preservative thimerosal.

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[5] (See the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 355(e)(3), and 21 C.F.R 10.30)

[6] Information gleaned from CRISP (Computer Retrieval of Information on Scientific Projects) is a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other research institutions and noted in Appendix D of "A Brief Analysis of Recent Efforts in Medical Mercury Induced Neurological and Autism Spectrum Disorders."

When faced with the facts that children in the first six months of life were receiving excessive levels of mercury through vaccines, the FDA has chosen to allow industry to determine its phase out period rather than to give them hard deadlines or refuse to allow its continued use at all.

Centers for Disease Control and Prevention

The CDC's failures are even more egregious. At every turn, when the CDC could have alerted the public and taken a strong stand against the use of thimerosal, they have chosen instead to promote flawed epidemiology studies as proof that no evidence of harm existed. If the uninformed public takes the statements on the CDC's website at face value, they could conclude that rigorous evaluations have been conducted and that no risks are associated with the use of thimerosal vaccines. Nothing could be further from the truth.

In July 2000 when you had the CDC before your Committee they made no mention of their own research looking at the thimerosal link. SafeMinds obtained relevant documentation through a Freedom of Information Act request that showed by December 1999 the CDC knew thimerosal could be linked to the increased incidence of neurodevelopmental disorders.

Using taxpayer resources, and access to the Vaccine Safety Datalink datasets, CDC research fellow Dr. Thomas Verstraeten and his team looked at the medical records of children in a number of HMOs to see if there was any truth to the thimerosal-autism hypothesis that had been proffered. Between February 2000 and November 2003 Dr. Verstraeten and his supervisors at the National Immunization Program produced four separate generations of an analysis designed to assess the impact of vaccine mercury exposures on neurodevelopmental disorders in children. With each generation, elevated and statistically significant risks were reduced and/or eliminated.

But before these four generations of reports were produced, Verstraeten conducted an earlier analysis of these issues in November and December of 1999. He never prepared a formal report on this work, but statistical tables obtained by Safe Minds in a FOIA request (and not previously analyzed) demonstrate large and statistically significant mercury exposure effects that in many cases exceeded the findings of the later reports.

These "Generation Zero" analyses followed a straightforward methodology that was relatively unaffected by biases applied later and was considerably more sensitive with respect to detecting mercury exposure effects than the later reports. Most notably, these initial analyses compared disease risk in the *highest exposure* population groups to disease risk in *zero exposure* population groups. In addition, the target study population had not yet been subject to numerous exclusions and adjustments applied later, the cumulative effect of which was to reduce the reported impact of mercury exposure on children's health outcomes.

The results of the Generation Zero analyses are striking and more supportive of a causal relationship between vaccine mercury exposure and childhood developmental disorders (especially autism) than any of the results reported later

- Relative risks of autism, ADD, sleep disorders and speech/language delay were consistently elevated relative to other disorders and frequently significant. Disease risk for the high exposure groups ranged from lows of 1.5 to 2 times to as high as 11 times the disease risk of the zero exposure group.
- Many other outcomes showed no consistent effect, while a few appeared to show a protective effect from vaccine mercury exposure (most likely children with these diagnoses were immunized later).
- The strongest effect was for the highest levels of mercury exposure at the earliest time of exposure, consistent with the idea that infant brain development is most sensitive to the earliest exposures.
- The elevated risk of autism for the highest exposure levels at one month ranged from 7.6 to 11.4 times the zero exposure level. This significant increased risk level corresponds to the tenfold increase in autism rates seen since vaccine mercury exposures increase starting in 1990.

The difference in these results in comparison to the later reports reveal a number of methodological choices that may have been powerful sources of bias in later generations of the analysis, including the exclusion of children with less than two polio vaccines. These children would have been most reliably in the zero exposure group, whereas children with two polio vaccines and also with low reported mercury exposure would be more likely to have exposure reporting errors and the elimination of zero exposure categories in general as the referent category for risk assessment as well as the reduction in the measured exposure in the highest category.

Even with alteration in the inclusion criteria the strong dose dependant associations between thimerosal exposure and several adverse neurological outcomes remained as described in an email from Dr. Verstraeten to his colleagues December 17, 1999 titled "It just won't go away" where Dr. Verstraeten informs the team of investigators that "these neurological outcomes are very much related (odds of having one when also having the other go from 20 to 100!) As you see some of the RR's increase over the categories and I haven't yet found an alternative explanation."

Their results were so striking and disturbing that the CDC would next call a private meeting away from the CDC complex and away from the public eye to discuss. At the now infamous "Simpsonwood Meeting" Dr. Verstraeten presented his findings to a closed group of CDC and HHS officials and selected outside experts many of whom were academic scientists with very close ties to vaccine manufacturers. This Committee, SafeMinds, and other vaccine injury advocacy organizations were not invited or even informed about this event; however, representatives from all five major vaccine manufacturers were present. Here, the beginning of a great injury to the public's trust in our nation's immunization programs would be crafted.

The Simpsonwood meeting, ostensibly designed to be a careful review of a CDC analysis on the impact of thimerosal-containing vaccines on child development, instead became a vehicle for making numerous deliberate choices that took positive findings in a single direction, towards insignificance. Recommendations made by CDC consultants reveal an active interest in suppressing the signal in any way possible and widespread interest in concealing the information.

This meeting provides evidence of the ways in which data can be manipulated in complex epidemiological analyses. Any population based epidemiological analysis involves numerous subtle choices with respect to study design and reporting which allow supervisors of such population based studies wide discretion in the results they choose to report, depending on whether they are interested in reporting a positive or negative finding. In their words and actions described below, CDC and NIP employees demonstrated clear biases against reporting positive results.

Dr. Rhodes made arguments to exclude the lowest exposure cases, claiming that the fact that their exposures were low suggested family behavior that made them unusual. The low rate of outcomes in this group of children, of course, added significance. Dr. Rhodes: Page 104: *"I am not advocating totally throwing them [the low mercury exposure group] away and never considering them in any analysis, but at least for now let's think if we can establish if there are differences in this group of 37 to 75* [micrograms of exposure, i.e., the middle exposure group], *then in a sense we really don't need them."*

He made arguments to exclude some cases that had unusually high exposures and outcomes at the same time. Any high exposure, high outcome group would support the signal. Dr. Rhodes: Page 105: *"The other thing that happens at NCK is that even a year or two years after the policy change has been made and all kids are supposedly receiving the combination, there is an odd, small group of kids that supposedly receives separate DTP and Hib (note: with more thimerosal) and an unusually high percentage of those kids are outcomes...For example, if 1,500 kids were receiving one vaccine combination in that month of birth and 20 were receiving some other, I have removed the 20 completely from the analyses."*

He made arguments to include non-comparable cases, all of which would serve to add "noise" that could obscure the signal. Dr Rhodes: Page 107: *"Now I take all those kids that Tom has excluded based on prematurity exclusion codes and throw them in. At one month I think there is some argument that is overdoing it. Throwing them all back in. I think there is a clear argument that is going too far, but that further brings things down. So you can push, I can pull. But there has been substantial movement from this very highly significant result down to a fairly marginal result."*

An official from the WHO suggests that there could be no value in examining the question regardless of the findings.

Dr. Clements: Page 247: *"I am really concerned that we have taken off like a boat going down one arm of the mangrove swamp at high speed, when in fact there was not enough discussion really early on about which way the boat should go at all. And I really want to risk offending everyone in the room by saying that perhaps this study should not have been done at all, because the outcome of it could have, to some extent, been predicted, and we have all reached this point now where we are left hanging, even though I hear the majority of consultants say to the Board that they are not convinced there is a causality direct link between Thimerosal and various neurological outcomes. I know how we handle it from here is extremely problematic."*

At the conclusion of the meeting a senior official of the National Immunization Program asks that the analysis remain secret. Dr. Bernier: Page 113: *"We have asked you to keep this information confidential. We do have a plan for discussing these data at the upcoming meeting of the Advisory Committee on Immunization Practices on June 21 and June 22. At that time CDC plans to make a public release of this information, so I think it would serve all of our interests best if we could continue to consider these data. The ACIP work group will be considering also. If we could consider these data in a certain protected environment. So we are asking people who have a great job protecting this information up until now, to continue to do that until the time of the ACIP meeting. So to basically consider this embargoed information. That would help all of us to use the machinery that we have in place for considering these data and for arriving at policy recommendations."*

Rather than take swift and aggressive measures to eliminate all exposures to thimerosal in children, the CDC delayed the publication of the data for years while conducting additional evaluations of the data. These career HHS officials in the highest positions of authority in vaccine programs, charged with protecting the public from harm, crafted and implemented a strategy that included suppressing their own findings of harm; and would re-run the data and re-write the study until all statistically significant correlations between thimerosal and neurological injury were wiped away. Their final conclusions, the message they would proclaim to the public was that no harm was found with the use of thimerosal in babies.

Subsequent attempts for independent review of the VSD data have been met with numerous obstacles. One completed study by Geier and Geier,[7] corroborated Verstraeten et al's initial suspicion of an apparent epidemiological link between Thimerosal and neurodevelopmental disorders, including autism. Unfortunately, since, and some suspect due to, the Geier's efforts, HHS and CDC have placed near impenetrable restrictions on access and study types related to VSD data, and such studies are no longer available for replication. This pattern of behavior constitutes malfeasance and should not be permitted to stand. It is time to remove the parties involved from their role in vaccine safety assessment and to subject the VSD data base to open and independent review.

Another area of concern regarding the CDC's lack of independence and objectivity in vaccine safety was brought to the attention of Congressman Weldon's office by Lujene Clark, President of NoMercury.org and Safe Minds. Each group has looked into this issue and been very concerned. In the Fall of 1999, just a few months after the joint statement calling for the removal of Thimerosal from childhood vaccines, a high-ranking CDC employee, Dr. Bob Chen, attended a meeting in Brighton, England created an the "Brighton Collaboration"[8] in collaboration with four of his vaccine colleagues, one of whom is an employee of Aventis Pasteur. The Brighton Collaboration's stated mission is "to facilitate the development, evaluation, and dissemination of high quality information about the safety of human vaccines." Their aim is to 'To develop

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[7] *Nuerodevelopmental Disorders after Thimerosal-Containing Vaccines: A Brief Communication*, Geier and Geier, Experimental Biology and Medicine, 2003

[8] "The Brighton Collaboration was founded by Robert Chen, Harald Heijbel, Tom Jefferson, Ulrich Heininger, and Elisabeth Loupi in 1999 at a meeting in Brighton, England. It was officially launched in autumn 2000. The Collaboration consists of volunteers from patient care, public health, scientific, pharmaceutical, regulatory and professional organizations coming from developed and developing countries." www.brightoncollaboration.org

globally accepted and implemented standardized case definitions of Adverse Events Following Immunization.'

While on the surface this may seem like a worthy cause, a number of legitimate concerns need to be fully addressed.

1. Are the CDC and its employees suborning their duties to a non-US non-governmental body?
2. The CDC (and WHO) began funding the Brighton Collaboration in 1999[9], before it was even legally formed. What process for approval did Dr. Chen go through to obtain this funding? How is Dr. Chen, a recognized leader in CDC's vaccine safety responsibilities allowed to form and lead a non-profit with direct correlations to his government duties? How did a CDC employee gain funding from the CDC for his outside activity? The Brighton website cites a salary structure for its leadership which begs the question, "Do Dr. Chen or other HHS employees receive double salaries?"
3. How much funding has the CDC (and WHO) provided each year since 1999? Who specifically within CDC and HHS approved this funding?
4. Brighton Collaboration now has offices at the CDC complex in Atlanta. Its employees appear to also be employees of the CDC? How is this possible?
5. The CDC Foundation, another non-government, not for profit, formed for the benefit to the CDC is raising money to funnel to Brighton. What process did these entities traverse to be afforded these privileges at CDC?
6. Since the Brighton Collaboration is a private vs. government entity, was one of the purposes of this organization to keep valuable vaccine safety data outside of public scrutiny?

SafeMinds after consulting with Nomercury.org submitted these and other questions to the Director of the CDC earlier this year and provided a copy to your office as well. Dr. Gerberding provided a response that indicates that she has not been fully and accurately informed on this matter. We are following up with a letter to point out the discrepancies in her responses. In the years since you first pointed out conflicts of interest, and in this year when the public first learned of the hundreds HHS employees that have financial ties to industry, getting this information out in the public is critical. I am providing you a copy of all of these letters and ask your assistance in getting the truth before the public.

Brighton is very troubling to parents who have cases before the Vaccine Injury Compensation Program for a number of reasons:

[9] "It obtained its first funding in 1999. The Brighton Collaboration is presently supported by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO). From 2000 until 2003, the Collaboration also received funding through the European Research Program for Improved Vaccine Safety Surveillance (EUSAFEVAC). In December 2003, the Brighton Collaboration Foundation was established by the University Children's Hospital Basel, Switzerland. The purpose of the Foundation is to protect and preserve public health by promoting immunization safety. The Foundation promotes the development and availability, of globally accepted, high quality scientific standards for research on and communication of immunization safety. The Foundation may also conduct immunization safety research itself or support such research projects." www.brightoncollaboration.org

1. Rumors abound that Brighton staff and 'volunteers' are being afforded access to the Vaccine Safety Datalink and other internal data when outside researchers are blocked.
2. Brighton while being promoted as 'independent' is actually a marriage of CDC/FDA employees and pharmaceutical representatives who are coming together to define what constitutes a vaccine adverse event and thus promote those definitions worldwide. One statement on their website states their intention to restrict doctors from reporting adverse events to vaccines that occur more than 48 hours after the delivery of a vaccine.
3. Because information developed and promoted by this entity will be supported by CDC and other government entities, the special masters within the Vaccine Injury Compensation Program will likely accept their findings without question and thus, as was the case with redefining what constitutes encephalopathy, families with vaccine injured children will not receive compensation in this program.
4. From a different but equally important view, the international community is being drawn in to this and may feel compelled to 'volunteer' their time and resources in order to stay in good graces with the CDC and WHO.

Given these actions, which the community is just this year learning about, combined with CDC's handling of the Vaccine Safety Link data, we see not only failure, but intentional actions to hide the truth.

On a good note, on August 30th, 2004 CDC approved a research-funding request from SafeMinds to investigate mechanisms of thimerosal toxicity. This funding will go to further research efforts of Dr. Hornig at Columbia University and Dr. James at the University of Arkansas. We applaud this award and appreciate the opportunity to further this important research. We also hope this is a potential harbinger of a redirection of CDC tone and focus in this discussion. While every research dollar is appreciated, it is still a vastly under-funded area.

Institute of Medicine

In 2001, the CDC and its Office of the National Immunization Program (NIP), contracted with the Institute of Medicine to create the Immunization Safety Review Committee in order the scientific evidence regarding a number of vaccine injury hypothesis including the correlation between reception of Thimerosal containing vaccines and the onset of neurodevelopmental disorders including autism.

The IOM's first report on Thimerosal was issued in October of 2001 and addressed the question if exposure to thimerosal containing vaccines could be associated with adverse neurodevelopmental disorders. The committee concluded that the evidence was inadequate to either accept or reject this hypothesis but went on to find the hypothesis "biologically plausible" and called for a clear and scientifically sound path for the requisite research necessary to finding the answers. That path included epidemiology, but also called for animal model, clinical, case study and other relevant research in keeping with the tenets of good science. The committee went even further to recommend that infants, children and pregnant women should not be exposed to thimerosal containing vaccines. This recommendation was not embraced by our Federal agencies.

Although the committee had issued a previous report on thimerosal in 2001, at the request of CDC, the committee was again called to review the issue in advance of causation hearings scheduled for later in the year. Unfortunately, at the time of the hearing, there was little additional science available for review, outside of population based epidemiological studies. In stating the charge to the committee, CDC chose to focus the investigation on autism alone instead of a broad range of adverse neurological outcomes previously considered as well as to place an emphasis on epidemiological investigations. Rather than reprimand the agency for its failures to adequately address the research recommendations in the 2001 report, the IOM would (1) accept a narrowing of their inquiry to autism alone and (2) would base its final conclusions on epidemiological research proven to be flawed.

On May 18th the Institute of Medicine's Immunization Safety Review Committee issued their final report which found that the biological mechanisms presented to the committee, including thimerosal's ability to induce DNA damage apopotosis in neurons, disrupt methionine synthase pathways, a model of autism induced with vaccine level exposure to thimerosal in an autoimmune mouse, elevated levels of mercury in children with autism after challenge with a chelating agent in comparison to controls, along with data that children with autism are not able to effectively excrete mercury theoretical at best. They concluded that the body of epidemiological evidence favors a rejection of a causal relationship between vaccine thimerosal exposure and autism.

A causal relationship between autism and vaccinations cannot be proved or rejected based solely on evidence from population-based epidemiologic studies. Epidemiological studies, by definition, are not designed to prove causality; they can only provide only statistical associations. Therefore, the committee's conclusion that the "body of epidemiologic evidence favors rejection of a causal relationship..." has no scientific meaning.

The committee admits in their report that population-based studies would not be able to detect subpopulations that could be genetically more vulnerable to mercury at lower doses than normal. The majority of children without the genetic susceptibility would simply "dilute out" the minority of susceptible children. "The committee recognizes that this line of reasoning as a theoretical explanation for the data presented in this report ..." (i.e., their conclusion of no association). The whole concept of identifying a *direct causal relationship* between vaccinations and autism may be impossible by definition – so the conclusion of "no association" would be inevitable and unavoidable. The mercury exposure is at best a "trigger" not the gun.

The conclusion that the available biological hypotheses for a causal relationship between autism and mercury "lack supporting evidence and are theoretical only" offers no justification for discouraging further research along these lines of investigation. All scientific hypotheses are "theoretical" by definition. By their own admission in the report, an untested and plausible biologic explanation for a causal association is the genetic susceptibility theory – the one theory that could explain their inability to detect an association in their population-based approach. Why was this not emphasized as a worthy hypothesis to explore?

The CDC's National Immunization program (NIP) has once again turned to the IOM for assistance. Just last month the first meeting of a panel was conducted to look at if and how to make the VSD information available to outside investigators and whether or not the CDC should make 'preliminary' data available. Dr. Bob Chen, who takes credit for creating the VSD program, was noticeably absent from this public meeting. How can the IOM be expected to do its job, if the CDC does not bring before the Committee to answer questions, those directly responsibility for these activities?

I would like to bring to your attention that one CDC employee in presenting information to this panel made grossly inaccurate statements in an attempt to excuse the lack of a well designed and executed program for outside research access. Dr. Roger Bernier, who has been before this committee, indicated that the CDC 'rushed' to put together the VSD sharing program (under Congressional pressure) when in fact the agency had a decade to develop a program, and after your intervention still took two years to design what has turned out to be a cumbersome sharing program. His statements were so blatantly false that another CDC staff person intervened to clarify and a former member of your staff further corrected the record during public comment.

SafeMinds joined a number of other organizations in calling upon the IOM panel to push for transparency and open access. We remain cautious and hopeful.

Funding Deficits at the National Institutes of Health

Access to data is important, but access means nothing if you do not have the resources to conduct research. The very reason taxpayers support significant resources ($27 billion) be provided to the National Institutes of Health (NIH) is to conduct research, free of industry or other outside influence, to get timely answers to important health related questions.

Since the mid-1980s we have seen epidemic increases in the rates of autism, yet the NIH and other health agencies have been slow to respond.

In 1997 the NIH was investing only $22 million on autism research. This covered therapeutic interventions, genetic research, and everything in between. That research investment has increased five-fold but remains woefully inadequate:

NIH Funding of Autism Research

Fiscal Year:	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**(estimated)
Funding (in millions):	**40**	**52**	**56**	**65**	**93**	**96**	**99**

The NIH's efforts to conduct and fund studies evaluating Thimerosal have been at times misdirected and continue to be inadequate given the severity of the potential risk associated with the discovery in 1999 that 8,000 children a day were being exposed to potentially dangerous levels of mercury. This premier $27 Billion biomedical institution comprised of 27 Institutes and Centers has to date failed to provide evidence to confirm that they have made this matter a priority or that they remain open-minded about the potential that thimerosal in vaccines may be linked to a novel form of autism – mercury-induced autism spectrum disorders. As the bastion

for high quality research, the one study the NIH's National Institute of Allergy and Infectious Diseases (NIAID) notes on in their May 2004 FAQ Public Page on NIAID-funded studies on the subject is the Rochester Study[10] as proof that thimerosal in vaccines is not linked to autism. In this investigation Pichichero measured blood levels of mercury in infants after exposure to thimerosal-containing vaccines.

There were a number of limitations in this investigation including a small sample size. Although the overall sample size was stated as 61 infants, there were only 33 exposed children who were used for the blood mercury assessment upon which the safety conclusions were made. One major shortcoming of a small sample size is the low chance of including infants who are especially sensitive to mercury's effects, or who may have detoxification difficulties. We know from the mercury literature that there is wide variability in the population in regard to mercury sensitivity and clearance. Since vaccines are given to virtually all infants, even if 1% retained mercury to a much greater degree than the "norm", this would represent a large number of injured children. The small sample size means that the study lacks sufficient power to establish safety claims. The sample was not randomly drawn, but was a convenience sample, and therefore not representative of all infants in terms of health status, socio-economic status, ethnicity, and other potentially important factors. The dose of mercury that the infants received was also much lower than what infants received during the 1990's. Blood levels for mercury were obtained days and often times weeks after the vaccine exposure. Given that the half-life of ethylmercury appears to be 6-7 days, virtually all, if not all, blood draws missed the peak blood concentrations of mercury. It is impossible to state what the peak values are if they were not measured. It is also impossible to calculate average blood concentrations unless peak concentrations are measured.

In spite of these limitations Pichichero makes the sweeping statement that "This study gives comforting reassurance about the safety of ethyl mercury as a preservative in childhood vaccines." The design and results of the study do not support these statements. In fact, the results suggest that thimerosal exposure from vaccines may have caused neurological damage in some children. Safe Minds questions the objectivity of the study authors, due to their ties to vaccine manufacturers, which may have resulted in a biased study design and biased interpretation of the results. Pichichero has an acknowledged financial tie to Eli Lilly, the developer of thimerosal and the main target of thimerosal litigation. He has also claimed financial ties to a number of vaccine manufacturers, including manufacturers of thimerosal-containing vaccines.

In the Pichichero study, there is one infant blood level out of the 17 2-month old blood samples (12%), which was 20.55 nMol/L, or 4.1 ppb. This infant had its blood drawn five days after the exposure and had received just 37.5 mcg/Hg. According to a letter Lancet the following month written by Dr. Neal Halsey of the Vaccine Safety Institute at Johns Hopkins, a dose of 62.5 mcg could well have resulted in a peak blood mercury level of 48.3nmol/l. Applying newly reported brain to blood partition ratio of 4.5 ng/ml (+/- 1.5) for thimerosal, predicted brain levels of mercury would be 217.35 ng/g.

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[10] Pichichero ME, Cernichiari E, Lopreiato J, and Treanor J. Mercury concentrations and metabolism in infants receiving vaccines containing thimerosal: a descriptive study. Lancet 360:1737-1741 (2002).

Given that Baskin *et al* (2003)[11] have documented DNA damage, caspase-3 activation, nuclear membrane damage and cell death in cultured adult human neurons and fibroblasts exposed to 201 mcg/l ethyl mercury (the lowest concentration tested) after 6 hours or less of incubation, routine vaccination practices during the 1990's levels may have resulted in neurodevelopmental injury to some infants. That the NIAID would fund a small and poorly controlled study and then promote the findings, as if it were meeting the gold standards of scientific rigor, despite the numerous letters to the editor of *Lancet* questioning the authors conclusions, is highly suspect.

While the entire research portfolio on autism spectrum disorders remains inadequate, the investment on thimerosal research remains miniscule. You have heard previously from scientists who for decades were funded by NIH and then once they asked for funding on vaccine adverse events, they were suddenly turned down. In the issue of thimerosal, what could have been accomplished in months has still not been accomplished five years later.

In previous hearings, HHS staff testified to you that they have nominated thimerosal to the National Toxicology Program[12] managed by the NIH's National Institute of Environmental Health Sciences. In their 2001 literature review and submission they conclude:

> *Limited data were found on the comparative toxicology of ethylmercury vs. methylmercury. One animal study directly compared the toxicity of these compounds in rats administered 5 daily doses (8.0 or 9.6 mg/kg) of equimolar concentrations of ethyl- or methylmercury by gavage. Tissue distribution, and the extent and severity of histological changes in the brain and kidney were assessed. Neurotoxicity of ethyl and methylmercury was similar, with higher levels of inorganic mercury observed in the brains of ethylmercury treated rats. Renal damage was greater in rats receiving ethylmercury. Although the data are limited, similar toxicological profiles between ethylmercury and methylmercury raise the possibility that neurotoxicity may also occur at low doses of thimerosal.*
>
> *Thimerosal is nominated to the NTP for further study to assess gaps in knowledge regarding toxicokinetics and the potential for neurodevelopmental toxicity. These gaps include comparative toxicity of ethyl- and methylmercury, the metabolism and elimination of ethylmercury compared with methylmercury, the effect of intermittent intramuscular doses of thimerosal from vaccines compared with chronic low dose oral exposure to methylmercury, and the susceptibility of the infant compared with the fetus to adverse effects from organicmercurials. In order to provide a more complete assessment of the toxicity of thimerosal during the critical period of neurodevelopment,*

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[11] Baskin, D., Ngo, Hop., and Didenko, V. Thimerosal induces DNA breaks, caspae-3 activation, membrane damage, and cell death in cultured human neurons and fibroblasts. *Toxicological Sciences*, 2003; **74:** 361-8.

[12] The National Toxicology Program (NTP) was established in 1978 by the Department of Health and Human Services (DHHS) to coordinate toxicological testing programs within the Department, strengthen the science base in toxicology; develop and validate improved testing methods; and provide information about potentially toxic chemicals to health regulatory and research agencies, the scientific and medical communities, and the public. The Program is administered by the NTP Director, who is also the Director of the NIEHS.

well-designed studies are needed to address these gaps in knowledge in appropriate animal model(s).[13]

Yet for Thimerosal, the NTP as of September 1, 2004, posts on their website the following information:

⇒ No bioassay studies are available evaluating standard toxicology and carcinogenesis
⇒ No reproductive studies are available
⇒ No developmental studies available
⇒ No immunology studies are available
⇒ In 1983, one *in vitro* salmonella study was conducted evaluating genetic toxicity for hamsters and rats (which was negative)

A further search of the NTP site finds that of the more than 8,000 chemicals in the market-place, zero have been approved for general toxicology study by the program. After more than 3 years of waiting, thimerosal has yet to hit the radar of the NTP. There are currently 31 chemicals with a project leader assigned and a study in design – thimerosal is not among them.

Existing Studies Support a Link Between Thimerosal Exposure and the Onset of Autism.

So is there scientific evidence to support parent's claim that after receiving thimerosal laden vaccines their children became ill? Is there evidence to validate that the presence of mercury in the bodies of young children, who also happen to be autistic, is of concern?

To those who remain open-minded, there is ample evidence to support these concerns. When HHS failed to fund the studies the IOM asked for, non-profit organizations, such as SafeMinds have funded or supplemented research at some of our country's most respected academic institutions. While then NIH spends less than $59 per autistic child on research, families who are paying tens of thousands of dollars out of pocket for the therapeutic care of their thimerosal-injured children have been forced to devote energy and resources to raise money research from art auctions, dinners, and t-shirt sales because for five years NIH and HHS have chosen not to make this a priority.

While HHS continues to state there is no evidence to support a link between thimerosal exposure and the onset of autism and that science does not yet know if ethylmercury is as toxic as methylmercury, the evidence has indeed been mounting.

A discourse between Congressman Dave Weldon, MD and Dr. David Baskin during the December 10, 2002 hearing of the Committee on Government Reform provides a fair analysis of this quandary:

[13] Thimerosal Nomination to the National Toxicology Program http://ntp-server.niehs.nih.gov/htdocs/Chem_Background/ExSumPDF/Thimerosal.pdf

Dr. Weldon. *I have a couple of questions for Dr. Baskin about ethyl mercury versus methyl mercury. I have had some people say that data on methyl mercury is fairly good, but we don't have good data on ethyl mercury. I take it from your testimony there is actually quite a bit of data on ethyl mercury and that it's as toxic as methyl mercury.*

Dr. Baskin. *There is more data, more and more data on ethyl mercury. The cells that I showed you dying in cell culture are dying from ethyl mercury. Those are human frontal brain cells. You know, there has been a debate about, well, ethyl versus methyl. But from a chemical point of view, most chemical compounds that are ethyl penetrate into cells better than methyl. Cells have a membrane on them, and the membrane is made of lipids, fats. And ethyl as a chemical compound pierces fat and penetrates fat much better than methyl. And so, you know, when I've began to work with some of the Ph.D.s in my laboratory and discuss this, everyone said, oh, gosh, you know, we've got to adjust for ethyl because it's going to be worse; the levels are going to be much higher in the cells. So, I mean, I think at best they're equal, but it's probably highly likely that they are worse. And some of the results that we are seeing in cell culture would support that...*[14]

Research by Clarkson, Magos and Meyers[15] and Gossel and Bricker's[16] determined, that ethyl mercury (thimerosal) has the capacity to attack and injure various neurodevelopment centers.

Boyd Haley, PhD, professor and chair at the University of Kentucky, Department of Chemistry provided clear and specific conclusions from his research and the evidence he has reviewed:

- Thimerosal is the major toxic component of most vaccines
- Thimerosal is a more potent inhibitor of many metabolic enzymes than is mercuric chloride
- Due to synergistic toxicity, thimerosal exposure through vaccines with aluminum should be considered quite capable of causing severe neurological and systemic damage.
- There appears to be a subset of the population that cannot effectively excrete mercury and are at a greater risk to exposures to mercury than are the general population. Genetic susceptibility is critical.
- Presence of other heavy metals, antibiotics, etc. may enhance the toxicity of thimerosal. Synergistic toxicities must be considered.
- Estrogen decreases thimerosal toxicity whereas testosterone increases the toxicity. Gender effects are involved.

In 2003, Holmes et al[17] published a paper showing that that lower overall rate of (excreted) mercury in the infants' hair for children diagnosed with autism. This finding strongly supported the hypothesis connecting autistic children's inability for excreting mercury, and as a precursor

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[14] Vaccines and the Autism Epidemic: Reviewing the Federal Governments Track Record and Charting a Course for the Future, Serial No. 107-153

[15] Thomas W. Clarkson, Ph.D., Laszlo Magos, M.D., and Gary J. Myers, M.D., *The Toxicology of Mercury — Current Exposures and Clinical Manifestations*, N Engl J Med 2003;349:1731-7.

[16] Gossel TA, Bricker JD. Principles of clinical toxicology. 2nd ed. New York: Raven Press, 1990.

[17] Reduced Levels of Mercury in First Baby Haircuts of Autistic Children, International Journal of Toxicology, 22:277–285, 2003

to mercury induced neurotoxicity and subsequent development disorders. Non-autistic children were found to have substantially higher mercury levels in their first cuts, purporting that their excretion capacity for mercury is less hindered, at least in comparison to the capacity of autistic children.

Dr. H. Vasken Aposhian, provided a similar perspective to the IOM in February: He put forward the possibility that there is an efflux impairment to which thimerosal is introduced into an unfavourable environment. Thimerosal would then be a final insult or "trigger" leading to autism.[18] The second postulate Aposhian put forward relies on the efflux impairment, but provides that the thimerosal introduction simply provides an increased mercury burden in the child. This postulate provides that the thimerosal exacerbates pre and post expected environmental exposure, putting the mercury burden over the threshold to neurotoxicity. Only through research can these questions be answered. Supportive to Aposhian's presentation were findings that "thimerosal pharmacokinetics obtained using non-autistic children are not the same as those expected for autistic children."[19] This furthered not only the issue of an efflux disorder, but to the variance in kinetics involved.

Bradstreet presented data to the IOM showing that single nucleotide polymorphism found in children with autism spectrum disorders provides the mapping from exposure to injury. Specifically, SNP's inhibited by thimerosal involving methylation and sulfation disallow a "normal process" for mercurial excretion. This event creates and maintains the elevated mercury body burden, which provides for the neurotoxic atmosphere, thus providing the architecture for neurodevelopmental injury resulting in injuries such as autism spectrum disorders.

What Bradstreet and James have accomplished is the initial recognition and mapping to the trigger mechanism(s) involved between the thimerosal (mercury) exposure and the end stage resultant disease. In reviewing the history of research regarding this issue, like so many other medical finds, it has been a process of reverse engineering. First was the recognition of the epidemic; next the suggested likeness between mercury poisoning and autism spectrum disorders; then the potential ties discovered through efforts in epidemiology; and now the causal trigger mechanism/event.

Deth et al,[20] found that "Neurodevelopment toxins, such as ethanol and heavy metals [thimerosal], interrupt growth factor signaling, raising the possibility that they might exert adverse effects on methylation..."Our findings outline a novel growth factor signaling pathway that regulates MS activity and thereby modulates methylation reactions, including DNA methylation. The potent inhibition of this pathway by ethanol, lead, mercury, aluminum and thimerosal suggests that it may be an important target of neurodevelopmental toxins."

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[18] Immunization Safety Review: Meeting 9: Aposhian Presentation, http://www.iom.edu/includes/dbfile.asp?id=18390 - Slide 16

[19] Immunization Safety Review: Meeting 9: Aposhian Presentation, http://www.iom.edu/includes/dbfile.asp?id=18390 - Slide 18

[20] M Waly, H Olteanu, R Banerjee, S-W Choi, J B Mason, B S Parker, S Sukumar, S Shim, A Sharma, J M Benzecry, V-A Power-Charnitsky and R C Deth *"Activation of methionine synthase by insulin-like growth factor-1 and dopamine: a target for neurodevelopmental toxins and thimerosal"*, Molecular Psychiatry, April 2004, Volume 9, Number 4, Pages 358-370

What Deth et al are continuing is a the building of the path to understanding of the role thimerosal plays in interruption of various developmental processes which lead to neurological development disorders, including autism.

Furthermore, Burbacher et al's[21] research effort investigating mercury blood levels in primates exposed to vaccine levels of methyl mercury and ethyl mercury provides that there are clear differences between ethyl and methyl mercury in blood and tissue levels over time. Unlike Dr. Sager's presentation of Burbachers primate research data at both CDC's Advisory Committee for Immunization Practice (ACIP) meeting on June 19th, 2003 and at the Institute of Medicine meeting held February 9th, 2004, I was surprised to find that earlier data presentations were incorrect and that the take home message that there was little accumulation of mercury in the brain of the primates dosed with thimerosal may not be a correct assumption. According to Dr. Burbacher's presentation[22] at a recent EPA sponsored symposium on mercury, the half life of mercury in the brains of primates dosed with thimerosal is 28 days, not 18 days as presented previously by Dr. Sager. And even more concerning is additional data which found that ethyl mercury more rapidly converted to toxic form of mercury in the brains of the primates which resulted in increasing levels of inorganic mercury. Once mercury converts to its inorganic form in the brain it is very difficult for it to be removed. Per Dr. Burbacher, this new data directly contradicts recent assertions made by Magos regarding the lower neurotoxic character of thimerosal relative to methylmercury.

This project, funded by NIAID, has forwarded nearly as many questions as it has answered. Specifically, while the mercury/blood level modeling has been mapped, the true levels, and increased propensity, for ethyl mercury to cross, and potentially to remain past, the blood-brain barrier. A request by the researchers to fund further study this issue, given the findings promoting caution to the use of ethyl mercury (thimerosal), has to date gone unfulfilled, and may need to be accomplished privately to provide further answers.

The next recently released study is from the Mailman School of Public Health at Columbia University. In this study,[23] Hornig et al looked at the effects of vaccine level thimerosal exposure on mice with a specific genetic susceptibility. This research postulate was created following the increasing body of scientific evidence promoting that the Thimerosal-NDD link is predicated upon certain genetic predispositions/genomic defects, which refer to autoimmune disease sensitivity.

Hornig et al found that the selected mice universally showed an implication of "genetic influences" that led to responses and activities that mimic those found in Autism Spectrum Disorders (including growth retardation, hypoactivity, social withdrawal, gross motor coordination, repetitive motions/movements, confusion or dissociation with familiar surrounds,

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[21] Burbacher, Shen, Clarkson, "Comparative Toxicokenetics of Methyl mercury and Thimerosal in Infant *Macca fasicularis*" presentation to Institute of Medicine, Immunization Safety Review Committee, 9 February 2004

[22] "Mercury in Macaque Infants following Oral Ingestion of Methylmercury or Intramuscular Injection of Vaccines Containing Thimerosal" presented by Thomas Burbacher, PhD.EPA Symposium on Mercury: Medical and Public health Issues, April 28-30, 2004. Tampa, Florida.

[23] Hornig, Chian, Lipkin, Molecular Psychiatry (2004), 1–13, *Neurotoxic effects of postnatal thimerosal are mouse strain dependent*

and other dysfunctional behaviours). Hornig et al's research also found physiological effects relevant to the brain and cranium in the creation of abnormalities resultant from vaccine level thimerosal exposure.

What all of the arena's researchers, regardless of position, are in agreement is the need for additional research to follow these matters through, for better understanding, potential treatments, and establishing policies and practices which will reverse the current epidemic trend.

What is being done to address these concerns?

Office of Special Counsel

The Office of Special Counsel (OSC) is an independent investigative and prosecutorial agency and operates as a secure channel for disclosures of whistleblower complaints and abuse of authority. Its primary mission is to safeguard the merit system in federal employment by protecting federal employees and applicants from prohibited personnel practices, especially retaliation for whistleblowing. OSC also has jurisdiction over the Hatch Act and the Uniformed Services Employment and Reemployment Rights Act.

Earlier this year, individuals within the thimerosal-induced autism community contacted the OSC out of concern that individuals within HHS knew that harm was possible and that they have acted to cover up the truth in order to protect their careers and their friends in industry. After an extensive review of the data, in May 2004, the Office of Special Counsel wrote to Senator Judd Gregg and Congressman Joe Barton asking them in their capacity as Chairman of the relevant legislative committees to investigate. Special Counsel Scott Bloch states in his letter," ...based on the publicly available information...it appears there may be sufficient evidence to find a substantial likelihood of a substantial and specific danger to public health caused by the use of thimerosal/mercury in vaccines because of its inherent toxicity. Due to the gravity of the allegations, I am forwarding a copy of the information disclosed to you in your capacity as Chairmen of the Senate Committee and House Committee with oversight authority for HHS. I hope that you will review these important issues and press HHS for a response to this very serious public health danger...I believe these allegations raise serious continuing concerns about the administration of the nation's vaccine program and the government's possibly inadequate response to the growing body of scientific research on the public health danger of mercury in vaccines. The allegations also present troubling information regarding children's cumulative exposure to mercury and the connection of that exposure to the increase in neurological disorders such as autism and autism-related conditions among children in the U.S."[24,25]

The OSC took what I believe is an unusual step, they issued a press release publishing this letter, which stated that without a whistleblower the OSC could not move forward. It is our understanding that whistleblowers have come forward and the OSC investigation is active. The

[24] www.osc.gov/documents/press/2004/pr04_07.htm
[25] http://www.cbsnews.com/htdocs/pdf/oscpdf.pdf

OSC has the capacity to hold the individuals within HHS who have failed the American public responsible for their actions.

HR 4169

For more than two years now, the CDC and others within HHS have reported to Congress and the media that thimerosal is out of all the vaccines being given to children. However, this past year the CDC chose not to state a preference for the use of thimerosal-free vaccines in children, rather promoting the reintroduction of thimerosal into the pediatric vaccine schedule by recommending that all children over the age of six months receive flu vaccine of which some brands continue to contain thimerosal.

Responding to HHS's failure to get the mercury out, Chairman Burton joined the bipartisan effort of Congressman Dave Weldon and Congresswoman Carolyn Maloney in introducing. HR 4169, "The Mercury Free Vaccine Act of 2004". To date, there are 31 cosponsors. SafeMinds supports the passage of the bi-partisan Bill as well as the bills passed in Iowa and California. We hope that Governor Schwarzenegger will sign AB 2943 immediately. We also hope that the Congress, in its waning days of the 108th Congress will pass HR 4169.

Conclusions

Chairman, when you first began your oversight investigation into vaccine safety concerns you were accused of being 'anti-vaccine' – in fact, this is the first attack on the credibility of anyone who dares to ask questions regarding vaccine safety. It is important to state that neither SafeMinds, as an organization, nor myself as a parent and health care professional, is opposed to vaccination. Nor are the independent researchers involved in this research. The investigation you initiated in 1999 has raised awareness about the need for good communication between parents, health care providers and our Federal agencies.

Vaccine safety is an important public health issue. Concerns voiced by parents, physicians and the scientific community regarding vaccine safety issues must be addressed with thoughtful, complete and unbiased investigations. Because vaccines are so widely used and because state laws require that children be vaccinated to enter daycare or school, vaccine safety issues, even if theoretical in nature, deserve to be investigated to the fullest extent possible.

Your investigations have highlighted the paucity of science in the field of vaccine adverse events and have created interest among academicians who likely would not have risked their careers asking these tough questions.

Although the removal of Thimerosal in medical products, including vaccines, has taken over 5 years to accomplish, we may be starting to see some the effects of this policy decision. According to information[26] released in July 2004 by the California State Department of Developmental Services (DDS), California has experienced the first ever nine month sustained

[26] State of California Department of Developmental Services, Friday, July 2, 2004 Quarterly Client Characteristics Report Index For the end of June 2004

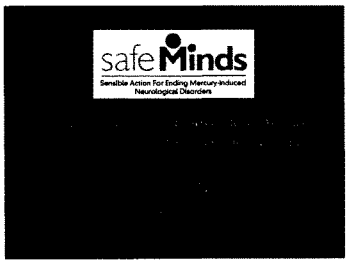
reduction in the numbers of professionally diagnosed new cases of full syndrome autism being added to California's developmental services system.

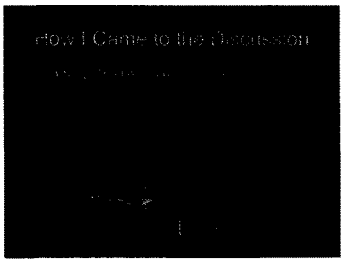
Not only did the most recent three consecutive quarter period produce the first sustained reduction in the 35 year history of California's developmental services system (197 fewer new cases then the previous October through June period), but the most current recently completed quarter, April 2004 through June 2004, produced the all time largest reduction of any quarter (108 less cases) in the history of the system.

What makes this historic development of this very recent reduction in new cases of autism so important is that those children from the birth cohorts of 1999 and 2000 are now entering the system. First with the year 1999 and much more so with year 2000, these are the widely recognized first two years of the beginning of the serious effort to substantially reduce the amount of the mercury containing preservative Thimerosal in childhood vaccines.

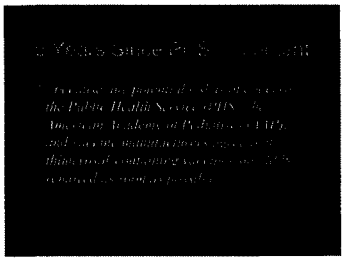
Thank you for the opportunity to present this information to the Subcommittee today.

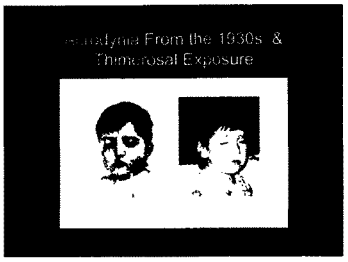
I would be happy to answer any questions.

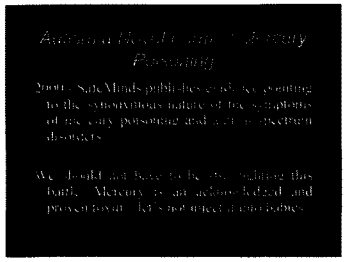

safeMinds
Sensible Action For Ending Mercury-Induced Neurological Disorders


How I Came to the Discussion


Thimerosal Injury




From the 1930s &
Thimerosal Exposure



Government Regulatory Failures Abound

Once the excessive levels of mercury exposure through vaccination was discovered those tasked with the role of protecting the public have repeatedly failed to aggressively respond ...

FDA's Failures Are Extensive

[illegible]

All Forms of Mercury Are Toxic

CDC's Failures Even More Egregious

- CDC repeatedly funded and promoted flawed epidemiology
- CDC has repeatedly refused to announce a preference for thimerosal-free vaccines for infants and is actively promoting the use of thimerosal in the flu vaccine recommended for pregnant women and children

CDC's Failures Even More Egregious (cont)

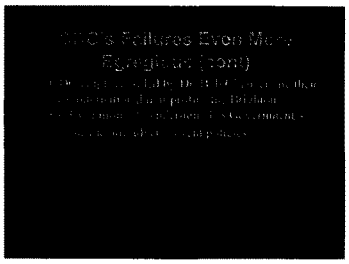
- CDC conducts VSD evaluation and finds proof of harm and doesn't immediately bring to the Congress or the public
- Instead CDC

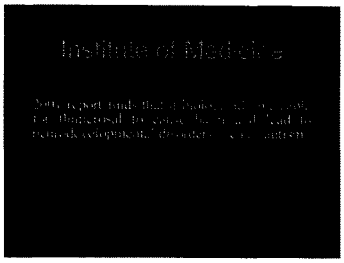
  (1) holds secret meetings to discuss study

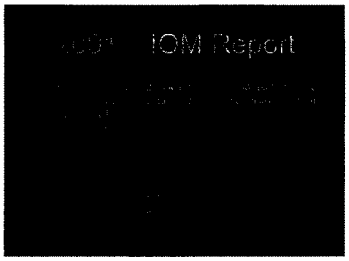
  (2) conducts at least 4 revisions of the study before publication – manipulating until no statistically significant correlation between thimerosal and injury is present in the data

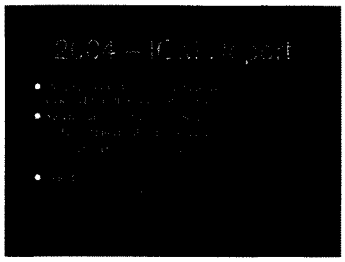
GENERATION ZERO ANALYSES

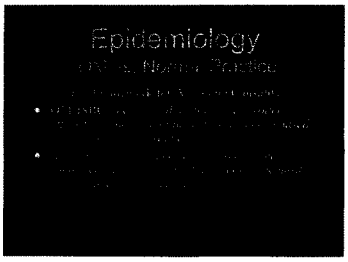
[illegible]

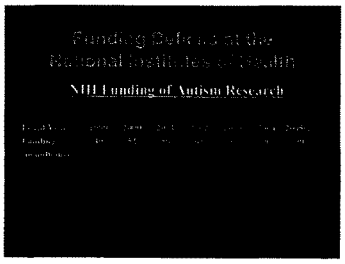


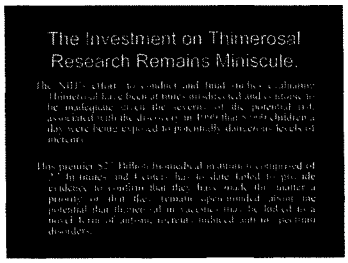

Institute of Medicine

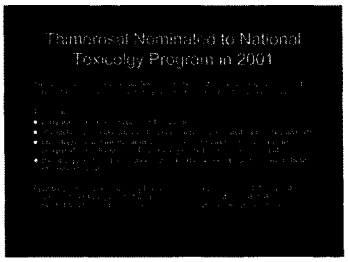

IOM Report

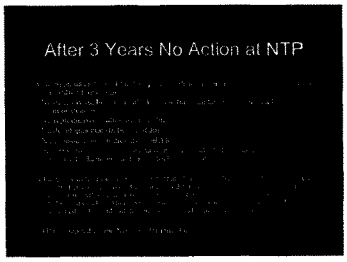



Epidemiology

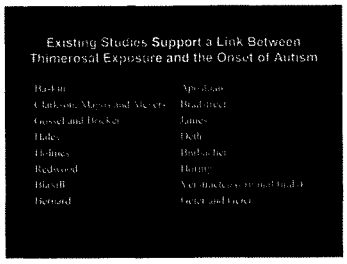

NIH Funding of Autism Research

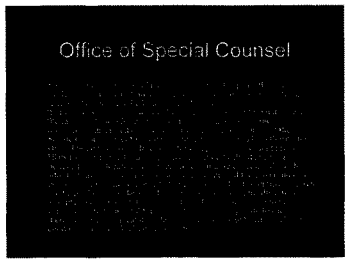

The Investment on Thimerosal Research Remains Miniscule.

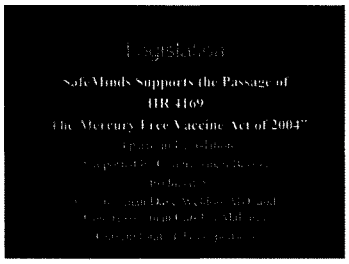

Thimerosal Nominated to National Toxicology Program in 2001

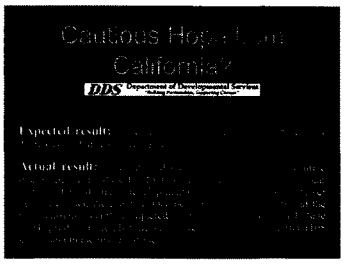

After 3 Years No Action at NTP

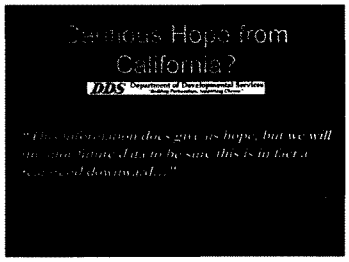

Is There Existing Science Supporting Thimerosal-Induced Autism?
Yes.


Existing Studies Support a Link Between Thimerosal Exposure and the Onset of Autism


Office of Special Counsel


Legislation
SafeMinds Supports the Passage of
HR 4169
The "Mercury Free Vaccine Act of 2004"


Cautious Hope from
California?
DDS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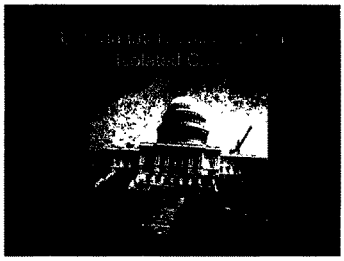

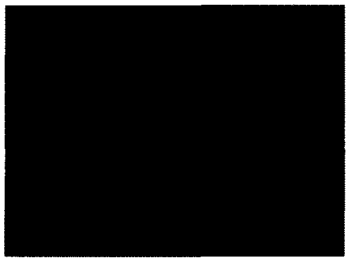

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Autism: a novel form of mercury poisoning

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Summary Autism is a syndrome characterized by impairments in social relatedness and communication, repetitive behaviors, abnormal movements, and sensory dysfunction. Recent epidemiological studies suggest that autism may affect 1 in 150 US children. Exposure to mercury can cause immune, sensory, neurological, motor, and behavioral dysfunctions similar to traits defining or associated with autism, and the similarities extend to neuroanatomy, neurotransmitters, and biochemistry. Thimerosal, a preservative added to many vaccines, has become a major source of mercury in children who, within their first two years, may have received a quantity of mercury that exceeds safety guidelines. A review of medical literature and US government data suggests that: (i) many cases of idiopathic autism are induced by early mercury exposure from thimerosal; (ii) this type of autism represents an unrecognized mercurial syndrome; and (iii) genetic and non-genetic factors establish a predisposition whereby thimerosal's adverse effects occur only in some children. © 2001 Harcourt Publishers Ltd

INTRODUCTION

Austic spectrum disorder (ASD) is a neurodevelopmental syndrome with onset prior to age 36 months. Diagnostic criteria consist of impairments in sociality and communication plus repetitive and stereotypic behaviors (1). Traits strongly associated with autism include movement disorders and sensory dysfunctions (2). Although autism may be apparent soon after birth, most autistic children experience at least several months, even a year or more of normal development – followed by regression, defined as loss of function or failure to progress (2–4).

The neurotoxicity of mercury (Hg) has long been recognized (5). Primary data derive from victims of contaminated fish (Japan – Minamata disease) or grain (Iraq, Guatemala, Russia); from acrodynia (Pink disease) induced by Hg in teething powders; and from individual instances of mercury poisoning (HgP), many occurring in occupational settings (e.g. Mad Hatter's disease). Animal and in vitro studies also provide insights into the mechanisms of Hg toxicity. More recently, the Food and Drug Administration (FDA) and the American Academy of Pediatrics (AAP) have determined that the typical amount of Hg injected into infants and toddlers via childhood immunizations has exceeded government safety guidelines on an individual (6) and cumulative vaccine basis (7). The mercury in vaccines derives from thimerosal (TMS), a preservative which is 49.6% ethylmercury (eHg) (7).

Past cases of HgP have presented with much interindividual variation, depending on the dose, type of mercury, method of administration, duration of exposure, and individual sensitivity. Thus, while commonalities exist across the various instances of HgP, each set of variables has given rise to a different disease manifestation (8–11). It is hypothesized that the regressive form of autism represents another form of mercury poisoning, based on a thorough correspondence between autistic and HgP traits and physiological abnormalities, as well as on the known exposure to mercury through vaccines. Furthermore, other phenomena are consistent with a causal Hg-ASD relationship. These include: (a) symptom onset shortly after immunization; (b) ASD prevalence increases corresponding to vaccination increases; (c) similar sex ratios of affected individuals; (d) a high heritability rate for autism paralleling a genetic predisposition to

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Hg sensitivity at low doses; and (e) parental reports of autistic children with elevated Hg.

TRAIT COMPARISON

ASD manifests a constellation of symptoms with much inter-individual variation (3,4). A comparison of traits defining, nearly universal to, or commonly found in autism with those known to arise from mercury poisoning is given in Table 1. The characteristics defining or strongly associated with autism are also more fully described.

Autism has been conceived primarily as a psychiatric condition; and two of its three diagnostic criteria are based upon the observable traits of: (a) impairments in sociality, most commonly social withdrawal or aloofness; and (b) a variety of perseverative or stereotypic behaviors and the need for sameness, which strongly resemble obsessive–compulsive tendencies. Differential diagnosis may include childhood schizophrenia, depression, obsessive–compulsive disorder (OCD), anxiety disorder, and other neuroses. Related behaviors commonly found in ASD individuals are irrational fears, poor eye contact, aggressive behaviors, temper tantrums, irritability, and inexplicable changes in mood (1,2,12–17). Mercury poisoning, when undetected, is often initially diagnosed as a psychiatric disorder (18). Commonly occurring symptoms include: (a) 'extreme shyness', indifference to others, active avoidance of others, or 'a desire to be alone'; (b) depression, 'lack of interest' and 'mental confusion'; (c) irritability, aggression, and tantrums in children and adults; (d) anxiety and fearfulness; and (e) emotional

Table 1 Summary comparison of traits of autism and mercury poisoning (ASD references in bold; *HgP references in italics*)

Psychiatric disturbances
Social deficits, shyness, social withdrawal (**1,2,130,131**; *21,31,45,53,132*)
Repetitive, perseverative, stereotypic behaviors; obsessive-compulsive tendencies (**1,2,43,48,133**; *20,33–35,132*)
Depression/depressive traits, mood swings, flat affect; impaired face recognition (**14,15,17,103,134,135**; *19,21,24,26,31*)
Anxiety; schizoid tendencies; irrational fears (**2,15,16**; *21,27,29,31*)
Irritability, aggression, temper tantrums (**12,13,43**; *18,21,22,25*)
Lacks eye contact; impaired visual fixation (HgP)/problems in joint attention (ASD) (**3,36,136,137**; *18,19,34*)

Speech and language deficits
Loss of speech, delayed language, failure to develop speech (**1–3,138,139**; *11,23,24,27,30,37*)
Dysarthria; articulation problems (**3**; *21,25,27,39*)
Speech comprehension deficits (**3,4,140**; *9,25,34,38*)
Verbalizing and word retrieval problems (HgP); echolalia, word use and pragmatic errors (ASD) (**1,3,36**; *21,27,70*)

Sensory abnormalities
Abnormal sensation in mouth and extremities (**2,49**; *25,28,34,39*)
Sound sensitivity; mild to profound hearing loss (**2,47,48**; *19,23–25,39,40*)
Abnormal touch sensations; touch aversion (**2,49**; *23,24,45,53*)
Over-sensitivity to light; blurred vision (**2,50,51**; *18,23,31,34,45*)

Motor disorders
Flapping, myoclonal jerks, choreiform movements, circling, rocking, toe walking, unusual postures (**2,3,43,44**; *11,19,27,30,31,34,39*)
Deficits in eye-hand coordination; limb apraxia; intention tremors (HgP)/problems with intentional movement or imitation (ASD) (**2,3,36,181**; *25,29,32,38,70,87*)
Abnormal gait and posture, clumsiness and incoordination; difficulties sitting, lying, crawling, and walking; problem on one side of body (**4,41,42,123**; *18,25,31,34,39,45*)

Cognitive impairments
Borderline intelligence, mental retardation – some cases reversible (**2,3,151,152**; *19,25,31,39,70*)
Poor concentration, attention, response inhibition (HgP)/shifting attention (ASD) (**4,36,153**; *21,25,31,38,141*)
Uneven performance on IQ subtests; verbal IQ higher than performance IQ (**3,4,36**; *31,36*)
Poor short term, verbal, and auditory memory (**36,140**; *21,29,31,35,38,87,141*)
Poor visual and perceptual motor skills; impairment in simple reaction time (HgP)/lower performance on timed tests (ASD) (**4,140,181**; *21,29,142*)
Deficits in understanding abstract ideas & symbolism; degeneration of higher mental powers (HgP)/sequencing, planning & organizing (ASD); difficulty carrying out complex commands (**3,4,36,153**; *9,18,37,57,142*)

Unusual behaviors
Self injurious behavior, e.g. head banging (**3,154**; *11,18,53*)
ADHD traits (**2,36,155**; *35,70*)
Agitation, unprovoked crying, grimacing, staring spells (**3,154**; *11,23,37,88*)
Sleep difficulties (**2,158,157**; *11,22,31*)

Physical disturbances
Hyper- or hypotonia; abnormal reflexes; decreased muscle strength, especially upper body; incontinence; problems chewing, swallowing (**3,42,145,181**; *19,27,31,32,39*)
Rashes, dermatitis, eczema, itching (**107,146**; *22,26,143*)
Diarrhea; abdominal pain/discomfort, constipation, "colitis" (**107,147–149**; *18,23,26,27,31,32*)
Anorexia; nausea (HgP)/vomiting (ASD); poor appetite (HgP)/restricted diet (ASD) (**2,123**; *18,22*)
Lesions of ileum and colon; increased gut permeability (**147,150**; *57,144*)

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lability. Neuroses, including schizoid and obsessive–compulsive traits, problems in inhibition of perservation, and stereotyped behaviors, have been reported in a number of cases; and lack of eye contact was observed in one 12-year-old girl with mercury vapor poisoning (18–35).

The third diagnostic criterion for ASD is impairment in communication (1). Historically, about half of those with classic autism failed to develop meaningful speech (2), and articulation difficulties are common (3). Higher functioning individuals may have language fluency but still show semantic and pragmatic errors (3,36). In many cases of ASD, verbal IQ is lower than performance IQ (3). Similarly, mercury-exposed children and adults show a marked difficulty with speech (9,19,37). In milder cases, scores on language tests may be lower than those of unexposed controls (31,38). Iraqi children who were postnatally poisoned developed articulation problems, from slow, slurred word production to an inability to generate meaningful speech; while Iraqi babies exposed prenatally either failed to develop language or presented with severe language deficits in childhood (23,24,39). Workers with Mad Hatter's disease had word retrieval and articulation difficulties (21).

Nearly all cases of ASD and HgP involve disorders of physical movement (2,30,40). Clumsiness or lack of coordination has been described in many higher functioning ASD individuals (41). Infants and toddlers later diagnosed with autism may fail to crawl properly or may fall over while sitting or standing; and the movement disturbances typically occur on the right side of the body (42). Problems with intentional movement and imitation are common in ASD, as are a variety of unusual stereotypic behaviors such as toe walking, rocking, abnormal postures, choreiform movements, spinning; and hand flapping (2,3,43,44). Noteworthy because of similarities to autism are reports in Hg literature of: (a) children in Iraq and Japan who were unable to stand, sit, or crawl (34,39); (b) Minamata disease patients whose movement disturbances were localized to one side of the body, and a girl exposed to Hg vapor who tended to fall to the right (18,34); (c) flapping motions in an infant poisoned from contaminated pork (37) and in a man injected with thimerosal (27); (d) choreiform movements in mercury vapor intoxication (19); (e) toe walking in a moderately poisoned Minamata child (34); (f) poor coordination and clumsiness among victims of acrodynia (45); (g) rocking among infants with acrodynia (11); and (h) unusual postures observed in both acrodynia and mercury vapor poisoning (11,31). The presence of flapping motions in both diseases is of interest because it is such an unusual behavior that it has been recommended as a diagnostic marker for autism (46).

Virtually all ASD subjects show a variety of sensory abnormalities (2). Auditory deficits are present in a minority of individuals and can range from mild to profound hearing loss (2,47). Over- or under-reaction to sound is nearly universal (2,48), and deficits in language comprehension are often present (3). Pain sensitivity or insensitivity is common, as is a general aversion to touch; abnormal sensation in the extremities and mouth may also be present and has been detected even in toddlers under 12 months old (2,49). There may be a variety of visual disturbances, including sensitivity to light (2,50,51,52). As in autism, sensory issues are reported in virtually all instances of Hg toxicity (40). HgP can lead to mild to profound hearing loss (40); speech discrimination is especially impaired (9,34,). Iraqi babies exposed prenatally showed exaggerated reaction to noise (23), while in acrodynia, patients reported noise sensitivity (45). Abnormal sensation in the extremities and mouth is the most common sensory disturbance (25,28). Acrodynia sufferers and prenatally exposed Iraqi babies exhibited excessive pain when bumping limbs and an aversion to touch (23,24,45,53). A range of visual problems has been reported, including photophobia (18,23,34).

COMPARISON OF BIOLOGICAL ABNORMALITIES

The biological abnormalities commonly found in autism are listed in Table 2, along with the corresponding pathologies arising from mercury exposure. Especially noteworthy similarities are described.

Autism is a neurodevelopmental disorder which has been characterized as 'a disorder of neuronal organization, that is, the development of the dentritic tree, synaptogenesis, and the development of the complex connectivity within and between brain regions' (54). Depressed expression of neural cell adhesion molecules (NCAMs), which are critical during brain development for proper synaptic structuring, has been found in one study of autism (55). Organic mercury, which readily crosses the blood–brain barrier, preferentially targets nerve cells and nerve fibers (56); primates accumulate the highest Hg-levels in the brain relative to other organs (40). Furthermore, although most cells respond to mercurial injury by modulating levels of glutathione (GSH), metallothionein, hemoxygenase, and other stress proteins, neurons tend to be 'markedly deficient in these responses' and thus are less able to remove Hg and more prone to Hg-induced injury (56). In the developing brain, mercury interferes with neuronal migration, depresses cell division, disrupts microtubule function, and reduces NCAMs (28,57–59).

While damage has been observed in a number of brain areas in autism, many nuclei and functions are spared (36). HgP's damage is similarly selective (40). Numerous studies link autism with neuronal atypicalities within the amygdala, hippocampi, basal ganglia, the Purkinje and

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Table 2 Summary comparison of biological abnormalities in autism and mercury exposure

Mercury exposure	Autism
Biochemistry	
Binds -SH groups; blocks sulfate transporter in intestines, kidneys (40,93)	Low sulfate levels (91,92)
Reduces glutathione availability; inhibits enzymes of glutathione metabolism; glutathione needed in neurons, cells, and liver to detoxify heavy metals; reduces glutathione peroxidase and reductase (97,100,161,162)	Low levels of glutathione; decreased ability of liver to detoxify xenobiotics; abnormal glutathione peroxidase activity in erythrocytes (91,94,95)
Disrupts purine and pyrimidine metabolism (10,97,158,159)	Purine and pyrimidine metabolism errors lead to autistic features (2,101,102)
Disrupts mitochondrial activities, especially in brain (160,163,164)	Mitochondrial dysfunction, especially in brain (76,172)
Immune system	
Sensitive individuals more likely to have allergies, asthma, autoimmune-like symptoms, especially rheumatoid-like ones (8,11,18,24,28,31,111,113)	More likely to have allergies and asthma; familial presence of autoimmune diseases, especially rheumatoid arthritis; IgA deficiencies (103,106–109,115)
Can produce an immune response in CNS; causes brain/MBP autoantibodies (18,111,165)	On-going immune response in CNS; brain/MBP autoantibodies present (104,105,109,110)
Causes overproduction of Th2 subset; kills/inhibits lymphocytes, T-cells, and monocytes; decreases NK T-cell activity; induces or suppresses IFNg & IL-2 (100,112,117–120,166)	Skewed immune-cell subset in the Th2 direction; decreased responses to T-cell mitogens; reduced NK T-cell function; increased IFNg & IL-12 (103,108,114–116,173,174)
CNS structure	
Selectively targets brain areas unable to detoxify or reduce Hg-induced oxidative stress (40,56,161)	Specific areas of brain pathology; many functions spared (36)
Accummulates in amygdala, hippocampus, basal ganglia, cerebral cortex; damages Purkinje and granule cells in cerebellum; brain stem defects in some cases (10,34,40,70–73)	Pathology in amygdala, hippocampus, basal ganglia, cerebral cortex; damage to Purkinje and granule cells in cerebellum; brain stem defects in some cases (36,60–69)
Causes abnormal neuronal cytoarchitecture; disrupts neuronal migration, microtubules, and cell division; reduces NCAMs (10,28,57–59,161)	Neuronal disorganization; increased neuronal cell replication, increased glial cells; depressed expression of NCAMs (4,54,55)
Progressive microcephaly (24)	Progressive microcephaly and macrocephaly (175)
Neuro-chemistry	
Prevents presynaptic serotonin release and inhibits serotonin transport; causes calcium disruptions (78,79,163,167,168)	Decreased serotonin synthesis in children; abnormal calcium metabolism (76,77,103,179)
Alters dopamine systems; peroxidine deficiency in rats resembles mercurialism in humans (8,80)	Either high or low dopamine levels; positive response to peroxidine, which lowers dopamine levels (2,177,178)
Elevates epinephrine and norepinephrine levels by blocking enzyme that degrades epinephrine (81,160)	Elevated norepinephrine and epinephrine (2)
Elevates glutamate (21,171)	Elevated glutamate and asparate (82,176)
Leads to cortical acetylcholine deficiency; increases muscarinic receptor density in hippocampus and cerebellum (57,170)	Cortical acetylcholine deficiency; reduced muscarinic receptor binding in hippocampus (83)
Causes demyelinating neuropathy (22,169)	Demyelination in brain (105)
Neurophysiology	
Causes abnormal EEGs, epileptiform activity, variable patterns, e.g., subtle, low amplitude seizure activities (27,31,34,86–89)	Abnormal EEGs, epileptiform activity, variable patterns, including subtle, low amplitude seizure activities (2,4,84,85)
Causes abnormal vestibular nystagmus responses; loss of sense of position in space (9,19,34,70)	Abnormal vestibular nystagmus responses; loss of sense of position in space (27,180)
Results in autonomic disturbance: excessive sweating, poor circulation, elevated heart rate (11,18,31,45)	Autonomic disturbance: unusual sweating, poor circulation, elevated heart rate (17,180)

granule cells of the cerebellum, brainstem, basal ganglia, and cerebral cortex (36,60–69). Each of these areas can be affected by HgP (10,34,40,70–73). Migration of Hg, including eHg, into the amygdala is particularly noteworthy, because in primates this brain region has neurons specific for eye contact (74) and it is implicated in autism and in social behaviors (65,66,75).

Autistic brains show neurotransmitter irregularities which are virtually identical to those arising from Hg exposure: both high or low serotonin and dopamine, depending on the subjects studied; elevated epinephrine and norepinephrine in plasma and brain; elevated glutamate; and acetylcholine deficiency in hippocampus (2,21,76–83).

Gillberg and Coleman (2) estimate that 35–45% of autistics eventually develop epilepsy. A recent MEG study reported epileptiform activity in 82% of 50 regressive autistic children; in another study, half the autistic children expressed abnormal EEG activity during sleep (84). Autistic EEG abnormalities tend to be non-specific and have a variety of patterns (85). Unusual epileptiform activity has been found in a number of mercury poisoning cases (18,27,34,86–88). Early mHg exposure enhances tendencies toward epileptiform activity with a reduced

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level of seizure-discharge amplitude (89), a finding consistent with the subtlety of seizures in many autism spectrum children (84,85). The fact that Hg increases extracellular glutamate would also contribute to epileptiform activity (90).

Some autistic children show a low capacity to oxidize sulfur compounds and low levels of sulfate (91,92). These findings may be linked with HgP because: (a) Hg preferentially binds to sulfhydryl molecules (-SH) such as cysteine and GSH, thereby impairing various cellular functions (40); and (b) mercury can irreversibly block the sulfate transporter NaSi cotransporter NaSi-1, present in kidneys and intestines, thus reducing sulfate absorption (93). Besides low sulfate, many autistics have low GSH levels, abnormal GSH-peroxidase activity within erythrocytes, and decreased hepatic ability to detoxify xenobiotics (91,94,95). GSH participates in cellular detoxification of heavy metals (96); hepatic GSH is a primary substrate for organic-Hg clearance from the human (40); and intraneuronal GSH participates in various protective responses against Hg in the CNS (56). By preferentially binding with GSH, preventing absorption of sulfate, or inhibiting the enzymes of glutathione metabolism (97), Hg might diminish GSH bioavailability. Low GSH can also derive from chronic infection (98,99), which would be more likely in the presence of immune impairments arising from mercury (100). Furthermore, mercury disrupts purine and pyrimidine metabolism (97,10). Altered purine or pyrimidine metabolism can induce autistic features and classical autism (2,101,102), suggesting another mechanism by which Hg can contribute to autistic traits.

Autistics are more likely to have allergies, asthma, selective IgA deficiency (sIgAd), enhanced expression of HLA-DR antigen, and an absence of interleukin-2 receptors, as well as familial autoimmunity and a variety of autoimmune phenomena. These include elevated serum IgG and ANA titers, IgM and IgG brain antibodies, and myelin basic protein (MBP) antibodies (103–110). Similarly, atypical responses to Hg have been ascribed to allergic or autoimmune reactions (8), and genetic predisposition to such reactions may explain why Hg sensitivity varies so widely by individual (88,111). Children who developed acrodynia were more likely to have asthma and other allergies (11); IgG brain autoantibodies, MBP, and ANA have been found in HgP subjects (18,111,112); and mice genetically prone to develop autoimmune diseases 'are highly susceptible to mercury-induced immunopathological alterations' even at the lowest doses (113). Additionally, many autistics have reduced natural killer cell (NK) function, as well as immune-cell subsets shifted in a Th2 direction and increased urine neopterin levels, indicating immune system activiation (103,114–116). Depending upon genetic predisposition, Hg can induce immune activation, an expansion of Th2 subsets, and decreased NK activity (117–120).

POPULATION CHARACTERISTICS

In most affected children, autistic symptoms emerge gradually, although there are cases of sudden onset (3). The earliest abnormalities have been detected in 4-month-olds and consist of subtle movement disturbances; subtle motor-sensory disturbances have been observed in 9-month-olds (49). More overt speech and hearing difficulties become noticeable to parents and pediatricians between 12 and 18 months (2). TMS vaccines have been given in repeated intervals starting from infancy and continuing until 12 to 18 months. While HgP symptoms, may arise suddenly in especially sensitive individuals (11), usually there is a preclinical 'silent stage' in which subtle neurological changes are occuring (121) and then a gradual emergence of symptoms. The first symptoms are typically sensory-and motor-related, which are followed by speech and hearing deficits, and finally the full array of HgP characteristics (40). Thus, both the timing and nature of symptom emergence in ASD are fully consistent with a vaccinal Hg etiology. This parallel is reinforced by parental reports of excessive amounts of mercury in urine or hair from younger autistic children, as well as some improvement in symptoms with standard chelation therapy (122).

The discovery and rise in prevalence of ASD mirrors the introduction and spread of TMS in vaccines. Autism was first described in 1943 among children born in the 1930s (123). Thimerosal was first introduced into vaccines in the 1930s (7). In studies conducted prior to 1970, autism prevalence was estimated, at 1 in 2000; in studies from 1970 to 1990 it averaged 1 in 1000 (124). This was a period of increased vaccination rates of the TMS-containing DPT vaccines among children in the developed world. In the early 1990s, the prevalence of autism was found to be 1 in 500 (125), and in 2000 the CDC found 1 in 150 children affected in one community, which was consistent with reports from other areas in the country (126). In the late 1980s and early 1990s, two new TMS vaccines, the HIB and Hepatitis B, were added to the recommended schedule (7).

Nearly all US children are immunized, yet only a small proportion develop autism. A pertinent characteristic of mercury is the great variability in its effects by individual, so that at the same exposure level, some will be affected severely while others will be asymptomatic (9,11,28). An example is acrodynia, which arose in the early 20th century from mercury in teething powders and afflicted only 1 in 500–1000 children given the same low dose (28). Studies in mice as well as humans indicate that susceptibility to Hg effects arises from genetic status, in some

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cases including a propensity to autoimmune disorders (113,34,40). ASD exhibits a strong genetic component, with high concordance in monozygotic twins and a higher than expected incidence among siblings (4); autism is also more prevalent in families with autoimmune disorders (106).

Additionally, autism is more prevalent among boys than girls, with the ratio estimated at 4:1 (2). Mercury studies in mice and humans consistently report greater effects on males than females, except for kidney damage (57). At high doses, both sexes are affected equally; at low doses only males are affected (38,40,127).

DISCUSSION

We have shown that every major characteristic of autism has been exhibited in at least several cases of documented mercury poisoning. Recently, the FDA and AAP have revealed that the amount of mercury given to infants from vaccinations has exceeded safety levels. The timing of mercury administration via vaccines coincides with the onset of autistic symptoms. Parental reports of autistic children with measurable mercury levels in hair and urine indicate a history of mercury exposure. Thus the standard primary criteria for a diagnosis of mercury poisoning – observable symptoms, known exposure at the time of symptom onset, and detectable levels in biologic samples (11,31) – have been met in autism. As such, mercury toxicity may be a significant etiological factor in at least some cases of regressive autism. Further, each known form of HgP in the past has resulted in a unique variation of mercurialism – e.g. Minamata disease, acrodynia, Mad Hatter's disease – none of which has been autism, suggesting that the Hg source which may be involved in ASD has not yet been characterized; given that most infants receive eHg via vaccines, and given that the effect on infants of eHg in vaccines has never been studied (129), vaccinal thimerosal should be considered a probable source. It is also possible that vaccinal eHg may be additive to a prenatal mercury load derived from maternal amalgams, immune globulin injections, or fish consumption, and environmental sources.

CONCLUSION

The history of acrodynia illustrates that a severe disorder, afflicting a small but significant percentage of children, can arise from a seemingly benign application of low doses of mercury. This review establishes the likelihood that Hg may likewise be etiologically significant in ASD, with the Hg derived from thimerosal in vaccines rather than teething powders. Due to the extensive parallels between autism and HgP, the likelihood of a causal relationship is great. Given this possibility, TMS should be removed from all childhood vaccines, and the mechanisms of Hg toxicity in autism should be thoroughly investigated. With perhaps 1 in 150 children now diagnosed with ASD, development of HgP-related treatments, such as chelation, would prove beneficial for this large and seemingly growing population.

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Health Journal / *By Tara Parker-Pope*

Controversial Study Reignites Debate Over Autism and Childhood Vaccines

JUST A FEW MONTHS after the nations' top medical adviser rejected a link between vaccines and autism, a mouse study has reignited the debate and raised new fears among parents considering vaccinations and flu shots for their kids.

For years, a cadre of parents and physicians have contended that thimerosal, an ethyl-mercury compound that has been one of the most widely used vaccine preservatives, is partly responsible for an apparent rise in autism in recent decades. But broad population studies haven't supported the claim. In May, a major report from the Institute of Medicine's Immunization Safety Review Committee, sought to put the debate to rest, rejecting a link between autism and vaccines.

But tomorrow, a congressional committee will review a June study from Columbia University, which found that a mercury preservative used in vaccines can indeed cause autism-like symptoms in a specific strain of mice. The research raises important questions about whether some people might be genetically vulnerable to the effects of thimerosal.

The study also raises questions about a new push by the Centers for Disease Control and Prevention to add flu shots to the immunization schedule for school-age kids. Thimerosal has been mostly phased out of childhood vaccines, which include shots for whooping cough and other illnesses. But the vast majority of flu shots given to both adults and children still contain the preservative. In addition, it's widely believed that many unexpired vials of thimerosal-containing childhood vaccines remain on the shelves of pediatricians' offices.

None of this is to say that parents should stop having their children vaccinated. Instead, critics of thimerosal say parents should insist on thimerosal-free vaccines and ask to check the label themselves before a child receives a shot.

Many researchers believe increased use of vaccines with thimerosal may help explain the alarming rise in autism in the U.S. which was just 1 in 2,500 children 20 years ago. Now CDC studies show the rate for autistic disorders in some areas to be as high as 1 in 150.

But the IOM report said an exhaustive review of the evidence doesn't support the claim that vaccines are to blame. The finding has sparked the ire of many autism researchers as well as parents who are convinced that vaccinations triggered autism in their kids. Among them is Congressman Dan Burton, an Indiana Republican, whose grandson developed autism five years ago after receiving shots containing thimerosal. Rep. Burton is chairman of the subcommittee that this week will hold hearings on the mouse study and other research. "We just need to get the mercury out of vaccinations," says Rep. Burton.

What is so frustrating to critics of the IOM report is that thimerosal is an entirely unnecessary ingredient. The mercury preservative typically is found in multi-dose vials to prevent contamination. But vaccines can be packaged in single doses and other preservatives can be used to protect multi-dose packs. Thimerosal remains in use in flu shots and adult vaccines mainly because of the cost of changing ingredients or switching to single-dose shots. "We have other ways to make vaccines safe," says Ellen Silbergeld, professor of environmental health sciences at Johns Hopkins Bloomberg School of Public Health.

Getting the Best Shot

Here are steps you can take to make sure your child receives a mercury-free vaccine:

- Ask for thimerosal-free vaccine.
- Check availability before appointment.
- Ask for vaccines in single-dose vials or syringes.
- Read manufacturer label or insert to check ingredients yourself.
- Look up common vaccines on www.fda.gov/cber/vaccine/thimerosal.htm.
- Consider intranasal flu vaccine for school-age kids.

The new mouse study bolsters the theory that genes involved in the immune system might make some people vulnerable to mercury—explaining why the vast majority of kids do fine after vaccines while a small number develop problems.

In the Columbia study, researchers administered thimerosal to four strains of young mice, injecting them with amounts comparable to those given to kids. Three of the mice strains were unaffected by thimerosal, but the fourth developed problems consistent with autism such as delayed growth, social withdrawal and brain abnormalities. The vulnerable mice were known to have a specific genetic susceptibility to mercury.

While a mouse study is far from conclusive, it's important to know that mice have long been a useful proxy for understanding human health. The researchers are close to developing a blood test to look for similar patterns in autistic children to see if the research translates to humans. Until more is known, says Mady Hornig, associate professor of epidemiology at Columbia's Mailman School of Public Health, "I think we should err on the side of caution and more thimerosal-free vaccine should be available."

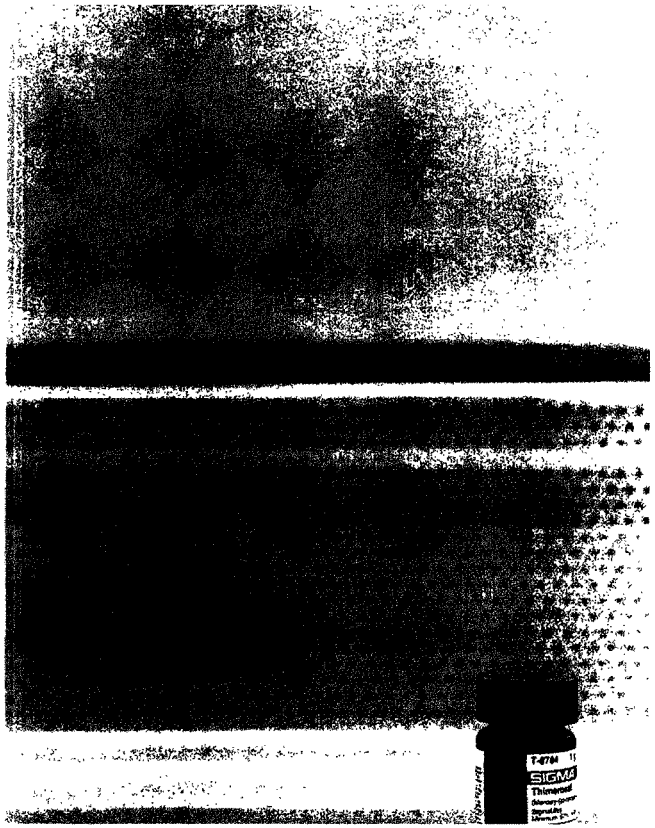
Other experts say the mouse study offers little insight into the issue, but is needlessly upsetting parents and could undermine the nation's childhood vaccination program. Unproven worries about autism and vaccines are "hypothetical" compared to "a very real risk of disease," notes Marie McCormick, professor of maternal and child health at Harvard School of Public Health and chairwoman of the IOM committee.

Parents concerned that a pediatrician may have an old vial of thimerosal-containing vaccine can politely ask to see the label. Most doctors understand that parents can be nervous about vaccinations, says Ian Lipkin, director of the Center for Immunopathogenesis and Infectious Diseases at Columbia University and co-author of the mouse study. In addition, you can check Food and Drug Administration charts listing vaccines and their thimerosal status at www.fda.gov/cber/vaccine/thimerosal.htm.

Many doctors and clinics may not have a supply of thimerosal-free flu shots. Calling in advance may give a doctor enough time to obtain a single-dose syringe. Another option is to ask for Flu-Mist, a nasal mist vaccine that doesn't contain thimerosal.

E-mail healthjournal@wsj.com and read my responses in Health Mailbox inside this section.

Journal Link: *Join a discussion with Health Journal columnist Tara Parker-Pope about the latest findings on autism, at* **WSJ.com/PersonalJournal**



The Big Antidote: Mercury

Is the nation's spiraling rate of autism caused by the mercury in vaccines? With over four thousand cases pending, a trillion dollars at stake, and public trust on the line, a firestorm is sweeping from the halls of science to the boardrooms of Big Pharma to the steps of the Capitol. Sarah Bridges spends nine months with a father-and-son team of researchers on the frontline.

The air in the meeting room had grown stale as the afternoon wore on, but Minnesota Attorney General Mike Hatch listened intently, puzzling his way through the data. Leaning forward at the head of the oak table that dominated the room, he asked, "Are you saying there is still mercury in vaccines today?"

After a quick glance at his attaché case, Dr. Mark Geier replied, "In several of them—we have the bottles here to show you."

"I thought the Federal and Drug Administration required it to be removed," countered Hatch.

Mark Geier sighed. "They *recommended* it be removed. Many of our children are still being injected with mercury at their well-baby checkups."

Mercury is the main component of thimerosal, an antibacterial preservative that until recently was used in most vaccines. It has become a lightening rod in an escalating debate over the cause of the nation's rising rates of autism. It has entangled parents, health care providers, legislators, attorneys, public health officials, and drug makers, prompting them to ask one central question: Is thimerosal the mark of colossal government negligence or merely a symbol of parental desperation?

This debate became more than a theoretical one for me the day I received a call from the office of Congressman David Weldon (R-Florida), asking me if I was writing anything about thimerosal. Stuart Burns, Weldon's deputy chief of staff, was calling in response to an article I wrote in *The Washington Post Magazine*, detailing the government's acknowledgement of my son's brain damage from a vaccine. Mr. Burns gave me the name of Dr. Mark Geier and Dr. Geier's son David, saying, "They are the only self-funded researchers publishing in peer-reviewed journals on thimerosal and autism, using CDC data. You should talk with them." Twenty-four hours later, I was on the phone with the Geiers. I was doubtful about what I'd hear as I dialed their number. We started speaking at 9:30 on a Saturday night. We didn't finish until after midnight.

In the course of that call—and a two-day visit to their home a few weeks later—I heard a story that sounded more like a whodunit than a typical scientific investigation. They detailed their evidence linking thimerosal with the autism epidemic, and it was compelling. I had to hear more and told them I'd come visit in order to fully understand the issue.

Almost everybody knows of someone with autism today—but it wasn't always like that. In the years between 1970 and the late '90s, the autism rates in America rose from 1 in 10,000 children to 1 in 166. The Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP) sent out an *Autism A.L.A.R.M.* to pediatricians across the country in March 2004, warning them that the disorder "is prevalent" and must be treated early and aggres-

Photography by Jason Gould

Mr. BURTON. Thank you, Ms. Redwood. I understand your deep concern about this, since you as well as my family have suffered from having an autistic child in the family. We appreciate your comments.

Dr. Fischer.

STATEMENT OF RICHARD FISCHER, D.D.S., INTERNATIONAL ACADEMY OF ORAL MEDICINE AND TOXICOLOGY

Dr. FISCHER. Good afternoon, Mr. Chairman and members of the committee and guests. My name is Rich Fischer, I'm a dentist.

Dental amalgam or silver mercury fillings contain 50 percent mercury, which is more toxic than lead, cadmium or even arsenic. These dental fillings contribute more mercury to body burden in humans than all other sources combined. In fact, the amount of mercury contained in one average size filling exceeds the U.S. EPA standard for human exposure for over 100 years.

Mercury vapor which escapes from these fillings is readily absorbed into the body, accumulates within all body tissues and has been shown to cause pathophysiology. In the case of pregnant women with mercury fillings, the mercury readily passes from her fillings into her lungs through her bloodstream through the placental barrier and into the developing child, whose central nervous system and immune system are especially vulnerable to this poison.

The fetus developing in the average American mother will be born into this world with more mercury from its mother's dental fillings alone than it will receive from all the vaccinations it receives during its first 5 years of childhood. And I would add, those vaccines, without the trace, that was with the full load of thimerosal.

Scientists around the world have come to realize that even minute amounts of mercury can cause permanent neurological harm to young children and developing fetuses. The EPA recently announced that 630,000 babies are born each year with too much mercury in their bodies, and that one woman of childbearing age in 12 has enough mercury in her system to put her at risk to giving birth to a retarded child.

In response, the FDA has issued advisories to pregnant women and women of childbearing age to reduce their dietary intake of those fish which are known to contain elevated levels of mercury, such as tuna, swordfish and shark. But according to leading toxicologists, including the World Health Organization, only 20 percent of mercury body burden in adults is derived from diet. In contrast, 80 percent is derived from dental fillings.

As of today, the FDA has yet to advise these same women whom they warned against eating fish to avoid having mercury fillings placed in their mouth. If 20 percent is a problem, why isn't 80 percent a bigger problem?

In 1976, the President and Congress directed the FDA to evaluate all medical devices intended for human use and to classify them according to safety and effectiveness. The FDA was also directed to "assure the safety and effectiveness of medical devices intended for human use." Dental amalgam has been the most widely

used dental device for over 150 years. Yet to date, the FDA has never accepted or classified mixed dental amalgam. I ask why.

In 1987, upon the advice of the FDA dental device panel, the FDA accepted not dental amalgam but its premixed and separate components, amalgam alloy as class 2 and dental mercury as class 1. Class 1 is for devices that present no risk of harm and therefore are subject only to general controls for good manufacturing procedures. That's right, the FDA classifies mercury, the most neurotoxic element on the planet, to be of equal risk to humans as toothbrushes and dental floss.

Neither amalgam alloy nor dental mercury can be placed into a tooth until they have been first mixed together. Forgetting the safety issue for a moment, why does the FDA classify them as devices when neither is effective? They cannot be an effective device until mixed together. One cannot put mercury into a cavity, it will just drip right out. Similarly, you can't put the amalgam alloy powder into a cavity, because it immediately washes out.

In 1991, the FDA director of dental devices declared that the reason the FDA cannot regulate mixed dental amalgam is because it is prepared by the dental clinician. Yet at the same time they do classify dental resins and dental cements, which also must be prepared by the clinician.

In 1998, the FDA ruled that mercury is not generally recognized as safe. However, it left dental mercury as a safe and effective class 1 dental device. Since all other medical uses of mercury have been banned, why should we assume that the only safe to implant it is in the human mouth?

Scrap amalgam, that unused portion of the filling material remaining after the filling material remaining after the filling is placed into a patient's tooth, must be handled as a toxic waste disposal hazard. It cannot be thrown in the trash or buried in the ground or incinerated. It must be stored in an airtight vessel until properly disposed of. How can we justify storing this same mixture inches from a child's brain stem and declare it harmless?

The International Academy of Oral Medicine and Toxicology applauds the efforts of this subcommittee in urging the dental profession to join the rest of the medical profession and abandon the use of mercury. Thank you.

[The prepared statement of Dr. Fischer follows:]

TESTIMONY BEFORE THE SUBCOMMITTEE ON HUMAN RIGHTS & WELLNESS

U.S. HOUSE OF REPRESENTATIVES – SEPTEMBER 8, 2004

Dental amalgam ("silver" mercury) fillings contain 50% mercury, which is more toxic than lead, cadmium, or even arsenic. These dental fillings contribute more mercury to the body burden in humans than all other sources (*e.g.* dietary, air, water and vaccines) combined (1,2,3). In fact the amount of mercury contained in one average filling exceeds the U.S. EPA standard for human exposure for over 100 years.

Mercury vapor which escapes from these fillings is readily absorbed into the body, accumulates within all body tissues, and has been shown to cause pathophysiology. In the case of pregnant women with mercury fillings, the mercury readily passes from her fillings into her lungs, through her blood stream, through the placental barrier and into the developing child, whose central nervous system and immune system are especially vulnerable to this poison. The fetus developing in the average American mother will be born into this world with more mercury – from its mother's dental fillings alone – than it will receive from all the vaccinations it receives during its first 5 years of childhood. Scientists around the world have come to realize that even minute amounts of mercury can cause permanent neurological harm to young children and developing fetuses.

The EPA recently announced that 630,000 babies are born each year with too much mercury in their bodies, and that one woman of childbearing age in 12 has enough mercury in her system to put her at risk of giving birth to a retarded child. In response the FDA has issued advisories to pregnant women and women of childbearing age to reduce their dietary intake of those fish, which are known to contain elevated levels of mercury, such as tuna, swordfish and shark. But according to leading toxicologists, including the World Health Organization, only 20% of mercury body burden in adults is derived from diet. In contrast 80% is derived from dental fillings.

As of today the FDA has yet to advise these same women whom they warned against eating fish to avoid having mercury fillings placed into their mouths. If 20% is a problem, then why isn't 80% a bigger problem?

In 1976 the President and Congress directed the FDA to evaluate all medical devices intended for human use and to classify them according to their **safety and effectiveness**. The FDA was also directed to "assure the safety and effectiveness of medical devices intended for human use." Dental amalgam has been the most widely used dental device for over 150 years. Yet, to date, the FDA has never accepted or classified mixed dental amalgam. I ask why?

In 1987 upon the advice of the FDA Dental Device Panel, the FDA accepted not dental amalgam but its pre-mixed and separate components, "Amalgam Alloy" as Class II and "Dental Mercury" as Class I. (Class I is for devices that present no risk of harm, and therefore are subject only to "General Controls" for good manufacturing procedures.) That's right. The FDA classifies mercury, the most neurotoxic element on the planet, to be of equal risk to humans as toothbrushes and dental floss.

Neither "Amalgam Alloy" nor "Dental Mercury' can be placed into a tooth until they have first been mixed together. Forgetting the safety issue for a moment, why does the FDA classify them as devices when neither is effective? They cannot become an "effective'

device until mixed together. One cannot put mercury into a cavity – it will immediately drip out. Neither can one place the powdered alloy into a cavity – it will immediately wash away.

In 1991 the FDA director of Dental Devices declared that the reason the FDA cannot regulate mixed dental amalgam is because it is prepared by the dental clinician. Yet at the same time they do classify dental resins (composite fillings) and dental cements, which must also be prepared by the dental clinician.

In 1998 the FDA ruled that mercury is not Generally Recognized as Safe (GRAS). However it left "Dental Mercury" as a safe and effective Class I Dental Device. Since all other medical uses of mercury have been banned, why should we assume that the only safe place to implant it is the human mouth?

Scrap amalgam, that unused portion of the filling material remaining after the filling is placed into a patient's tooth, must be handled as a toxic waste disposal hazard (4). It cannot be thrown in the trash, buried in the ground or incinerated. It must be stored in an airtight vessel until properly disposed of. How can we justify storing this same mixture inches from a child's brainstem and declare it harmless?

The International Academy of Oral Medicine and Toxicology applauds the efforts of this subcommittee in urging the Dental Profession to join the rest of the Medical Profession and abandon the use of mercury.

Respectfully submitted,

Richard D. Fischer, DDS, FAGD
Past President, International Academy of Oral Medicine & Toxicology

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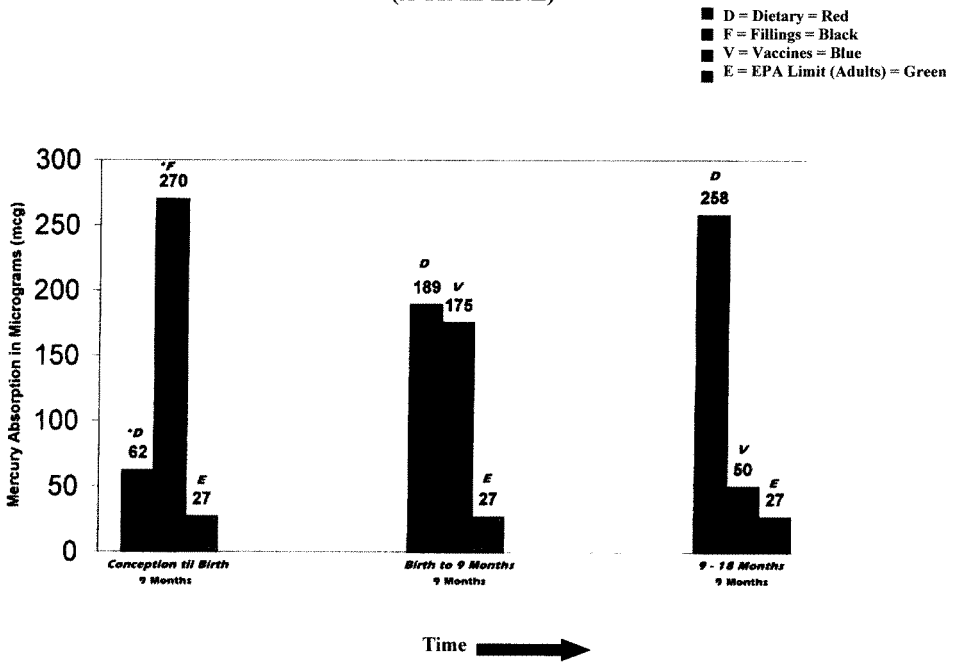
AVERAGE FETAL/INFANT ABSORBED DOSES OF MERCURY
(A TIME LINE)



***Contributed from Mothers Absorbed Doses Transferred to Fetus via Placenta**

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http://www.bioprobe.com/reviews.asp?review_id=18

SELECTED HEALTH SYMPTOM ANALYSIS OF 1569 PATIENTS BEFORE AND AFTER ELIMINATION OF THEIR MERCURY-CONTAINING DENTAL FILLINGS

% of Total	SYMPTOM	Total No.	No. Improved or Cured	%of Cure or Improvement
14%	ALLERGY	221	196	89%
05%	ANXIETY	86	80	93%
05%	BAD TEMPER	81	68	89%
06%	BLOATING	88	70	88%
06%	BLOOD PRESSURE PROBLEMS	99	53	54%
05%	CHEST PAINS	79	69	87%
22%	DEPRESSION	347	315	91%
22%	DIZZINESS	343	301	88%
45%	FATIGUE	705	603	86%
15%	GASTROINTESTINAL PROBLEMS	231	192	83%
08%	GUM PROBLEMS	129	121	94%
34%	HEADACHES	531	460	87%
03%	MIGRAINE HEADACHES	45	39	87%
12%	INSOMNIA	187	146	78%
10%	IRREGULAR HEARTBEAT	159	139	87%
8%	IRRITABILITY	132	119	90%
17%	LACK OF CONCENTRATION	270	216	80%
06%	LACK OF ENERGY	91	88	97%
17%	MEMORY LOSS	265	193	73%
17%	METALLIC TASTE	260	247	95%
07%	MULTIPLE SCLEROSIS	113	86	76%
8%	MUSCLE TREMOR	126	104	83%
10%	NERVOUSNESS	158	131	83%
08%	NUMBNESS ANYWHERE	118	97	82%
20%	SKIN DISTURBANCES	310	251	81%
09%	SORE THROAT	149	128	86%
06%	TACHYCARDIA	97	68	70%
04%	THYROID PROBLEMS	56	44	79%
12%	ULCERS & SORES (ORAL CAVITY)	189	162	86%
07%	URINARY TRACT PROBLEMS	115	87	76%
29%	VISION PROBLEMS	462	289	63%

762 patients utilized the FTFD Patient Adverse Reaction Report Form to individually report changes in their health directly to the FDA and the FTFD; Dr. Mats Hanson, Ph.D. reported on 519 Swedish patients; Henrik Lichtenberg,

Regulatory Status of Dental Amalgam - U. S. Food and Drug Administration (FDA)

- It has been reported that FDA has grand-fathered dental amalgam as an approved dental device. If this were true, dental amalgam would have an FDA classification and code, which is not the case. [1]

Dental amalgam has been the most widely used dental device for over 150 years. Yet, to this date, FDA has never accepted dental amalgam and assigned to it an appropriate FDA classification. One must wonder why FDA has refused to evaluate and classify this widely used dental device, in spite of their formal mandate to do so, and why it misleads the public by claiming dental amalgam was grand-fathered into acceptance. An explanation may be found by examination of the formally documented actions on dental amalgam.

Chronology of U. S. FDA Documented Activities on Dental Amalgam

- 1976: The President and Congress directed the Food and Drug Administration (FDA) to evaluate all medical devices intended for human use and to classify them according to their safety and effectiveness. FDA is also directed to *"assure the safety and effectiveness of medical devices intended for human use.* [2]
- 1975: FDA appoints "Panels" for each specialty of medicine, including dentistry. John W. Stanford, Ph.D. is appointed Chair of the Dental Device Panel. [3] (Note: At the time, Dr. Stanford was also Chair of the ADA Council on Dental Materials, Instruments and Equipment (CDMIE). The ADA Certifies "Dental Mercury" and "Amalgam Alloy" separately, but not dental amalgam which, it states, is a "reaction product" created by the dentist and therefore cannot be certified. [4])
- 1978: FDA Dental Device Panel requests that dental amalgam be excluded from the FDA definition of "Implant." FDA Commissioner declines request. [5]
- 1980: FDA Dental Device Panel refuses to recommend acceptance of mixed dental amalgam. It recommends acceptance of "Dental Mercury" and "Amalgam Alloy" as separate safe and effective dental devices. [6]
- 1987: FDA accepts "Amalgam Alloy (872.3050, Class II)" and "Dental Mercury (872.3700, Class I)" as separate, safe and effective dental devices. [7] (Note: Class I is for devices that present no risk of harm and, therefore, are subject only to "General Controls" for good manufacturing procedures. [2])
- 1991: FDA declares that they cannot regulate mixed dental amalgam because it is prepared by the dental clinician. [8]
- 1991: FDA Dental Products Panel holds hearing on the safety of dental amalgam. Presentation on safety on behalf of the American Dental Trade Association (ADTA, which includes the manufacturers of dental mercury and amalgam alloy) is given by John W. Stanford, Ph.D. [9]
- 1998: FDA rules that mercury is not Generally Recognized as Safe (GRAS) [10] However, it leaves "Dental Mercury" as a safe and effective Class I Dental Device. [Note: FDA, then, has accepted "Dental Mercury" as being non-toxic, while banning all other medical uses of mercury due to its toxicity.]
- 2003: FDA admits that it does not regulate or approve dental amalgam. It does "clear" and "accept for marketing" Dental Mercury and Amalgam Alloy, but does not approve them. [11]

Regulatory Status of Dental Amalgam - U. S. Food and Drug Administration (FDA)

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4. Letter, 22 May 1986: John W. Stanford, PhD. Secretary, CDMIE, ADA.
5. FR 43(146):32988, 28 Jul 1978.
6. FR 45(25):85963-86034, 30 Dec 1980.
7. FR 52(155):30082-30108, 12 Aug 1987.
8. Letter, 2 Apr 1991: Lillian Yin, PhD. Director, Ob-Gyn, ENT, Dental Devices; FDA
9. Statement of the American Dental Trade Association to the FDA Dental Products Panel, presented by John W. Stanford, Ph.D.; Update Report, Dental Amalgams, 3 December 1993.
10. FR 63(77):19799-19802, 22 Apr 1998.
11. Email correspondence, Susan Runner, DDS, MA, Dental Branch, CDRH, FDA, 5 Jan 2004.

Ex 2

United States of articles like or directly competitive with those produced by the firm contributed importantly to total or partial separation of the firm's workers, or threat thereof, and to a decrease in sales or production of the petitioning firm.

Any party having a substantial interest in the proceedings may request a public hearing on the matter. A request for a hearing must be received by the Chief, Trade Act Certification Division, Economic Development Administration, U.S. Department of Commerce, Washington, D.C. 20230, no later than the close of business of the tenth calendar day following the publication of this notice.

JACK W. OSBURN, JR.,
Chief, Trade Act Certification Division, Office of Planning and Program Support

[FR Doc.76-23563 Filed 8-11-76;8:45 am]

National Bureau of Standards

COMPUTER NETWORKING STANDARDS FOR LIBRARY AND INFORMATION SCIENCE COMMUNITY

Task Force Meeting

A task force has been established to address the problem of developing high-level computer-to-computer protocols for the nationwide interchange of information among existing and planned library and information science networks.

Members of the task force have been designated by the National Commission on Libraries and Information Science on the basis of their recognized experience and knowledge in the area of computer-to-computer data interchange for this class of applications and competence in developing related computer networking standard protocols. The task force will receive technical support from the NBS Institute for Computer Sciences and Technology.

The results of the task force effort, expected to be completed in about one year, will be provided directly to the American National Standards Institute, the American Library Association, and the American Society for Information Science for their respective consideration in development and adoption of standards directed specifically to the library and information science community.

All meetings of this task force will be open to the public; the purpose of this public notice is to announce the first task force meeting which will be held at the National Bureau of Standards, Gaithersburg, Maryland, on September 1 and 2, 1976. The meeting will convene on September 1 at 10 a.m. in Dining Rooms A and B of the NBS Administration Building; adjournment by 4 p.m. on September 2 is anticipated. A schedule for future meetings of the task force will be developed at this first meeting and published in the Federal Register.

For further information, interested members of the public may contact John L. Little, Institute for Computer Sciences and Technology, National Bureau of Standards, Washington, D.C. 20234, telephone: 301/921-3723.

Dated: August 9, 1976.

ERNEST AMBLER,
Acting Director.

[FR Doc.76-23820 Filed 8-11-76;8:45 am]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[Docket No. 76N-0235; DES 12301]

CHLORDIAZEPOXIDE AND CHLORDIAZEPOXIDE HYDROCHLORIDE PREPARATIONS

Drugs for Human Use; Drug Efficacy Study Implementation; Followup Notice and Opportunity for Hearing

Correction

In FR Doc. 76-19324 appearing in the issue of Tuesday, July 6, 1976, in the ninth line of the second full paragraph in the second column on page 27769, the word "a" should read "no".

[Docket No. 76N-0208]

MEDICAL DEVICES

Performance Standards Activities

The Food and Drug Administration (FDA) in this notice is advising all interested persons of its activities to date in the development of medical device performance standards and is indicating its intentions concerning the development and formal adoption of performance standards in the future.

On May 28, 1976, the President signed into law the Medical Device Amendments of 1976, Pub. L. 94-295. This legislation, which amends the Federal Food, Drug, and Cosmetic Act by adding new sections 513 through 521 (21 U.S.C. 360c through 360k), provides FDA with significant new authority to assure the safety and effectiveness of medical devices intended for human use. Among the most important provisions of the new amendments is the authority under section 514 to prescribe performance standards for medical devices.

As stated in section 513(a) of the act, devices requiring performance standards are those devices for which the general controls alone are insufficient to provide reasonable assurance of safety and effectiveness and for which there is sufficient information to establish a performance standard to provide such assurance. Devices requiring performance standards are also subject to the general control provisions of the act. These include existing controls prohibiting adulterated or misbranded devices, and new controls which include registration of device manufacturers; authority to ban certain devices; requirements respecting notification of risks and repair, replacement or refund; requirements to keep records and make reports; requirements restricting the sale, distribution or use of certain devices; and requirements with respect to good manufacturing practice.

A performance standard established under section 514 of the act for a device shall, among other things and where necessary to provide reasonable assurances of its safe and effective performance, include: (1) provisions respecting the construction, components, ingredients, and properties of the device and its compatibility with power systems and connections to such systems; (2) provisions for the testing of the device; and (3) provisions for the measurement of the performance characteristics of the device. The performance standard also shall, where appropriate, require the use and prescribe the form and content of labeling for the proper installation, maintenance, operation, and use of the device. Design-related requirements that are necessary to provide safe and effective performance or that reduce the likelihood of human error by improving device safety and efficacy may be included in a performance standard. See House Report No. 94-853, Medical Device Amendments, February 29, 1976 on page 26.

The Commissioner of Food and Drugs intends to issue a proposed procedural regulation in the FEDERAL REGISTER to explain the requirements of section 514, and describe how FDA will initiate, develop, promulgate, amend or repeal performance standards for medical devices. The procedural regulation to be proposed will apply to the development of all medical device standards, including standards for in vitro diagnostic products heretofore governed by the procedures set forth in Part 809 (21 CFR Part 809). In the interim, work on the development of in vitro diagnostic products standards will continue in accordance with the procedures in Part 809, to the extent that such procedures are consistent with the requirements of section 514 of the act.

Section 514 does not require that a procedural regulation governing standards development be effective at the time FDA initiates standards activities. The Food and Drug Administration will continue to proceed with the development of performance standards that may eventually be suitable for publication as proposed regulations according to procedures provided in section 514.

For several years, FDA has been engaged in activities designed to encourage the development of voluntary performance standards for medical devices. These efforts have been aimed primarily at developing criteria for measuring the performance characteristics of certain currently marketed devices that may present an unusual or serious risk of injury to persons treated with such products. Prior to the passage of the recent device amendments, FDA contemplated the possibility of adopting such standards as legal requirements for specific devices relying upon the general rule making authority conferred by section 701(a) of the act. Wholly apart from the possible need for enforceable legal requirements, however, FDA encourages and aided the development of device performance stand-

Ex 3

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

MEDICAL DEVICE CLASSIFICATION PROCEDURES

Notice to Manufacturers

In his consumer affairs message to the Congress on October 30, 1969, the President directed the Secretary of Health, Education, and Welfare to determine the scope and nature of additional legislative controls necessary to protect the public against unreasonable risk of injury or illness from medical devices. In accordance with this directive, the Secretary established the Study Group on Medical Devices under the chairmanship of Theodore Cooper, M.D., then Director of the National Heart and Lung Institute. The Study Group (Cooper Committee) report, entitled "Medical Devices: A Legislative Plan," was released in September 1970.

The report is available for public review at the office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852, during regular working hours Monday through Friday. The report may be purchased from the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, VA 22151.

The Cooper Committee report called for the enactment of new device legislation which would include provisions requiring the systematic review of existing medical devices for the purpose of grouping them into three categories: Those devices subject to general regulatory controls but exempt from standard setting and premarket approval; those for which standards should be set and enforced; and those requiring premarket approval.

In December 1971, following the recommendations of the Cooper Committee, the Secretary forwarded proposed medical device legislation to Congress. The legislation was introduced but no action was taken on it during that session of Congress. Legislation was again introduced in both the House of Representatives and the Senate in 1973. Hearings on the new medical device legislation were held by the Subcommittee on Health, Committee on Labor and Public Welfare of the Senate in September 1973, and by the Subcommittee on Public Health and Environment, Committee on Interstate and Foreign Commerce of the House of Representatives in October 1973. A medical device bill was passed in the Senate on February 1, 1974, but the House of Representatives did not enact device legislation during the 93rd Congress. During the 94th Congress, a medical device bill was introduced on March 26, 1975 in the House of Representatives. Soon after, on April 17, 1975, the Senate passed a medical device bill containing provisions comparable to those passed during the previous Congress and forwarded it to the House of Representatives for consideration.

Pending introduction and enactment of appropriate medical device legislation, the Secretary requested the Commissioner of Food and Drugs to develop an inventory of existing medical devices. The inventory was developed in 1973, primarily from information obtained from questionnaires sent to over 4,000 manufacturers in the United States. Approximately 2,000 replies were received. About 1,000 firms in the United States were identified as manufacturers of medical devices. A list of approximately 8,000 devices was compiled. That list subsequently has been broken down into the 14 classification panel specialty areas and is available through Bureau of Medical Devices and Diagnostic Products (BMDDP), HFK 100 (Division of Compliance) 5600 Fishers Lane, Rockville MD 20852.

The Secretary also requested the Commissioner to classify such devices into the three categories called for in the Cooper Committee report. The device classification process was preceded by the work of ad hoc committees composed of experts from the orthopaedic and cardiovascular specialty areas which were organized to develop and recommend general procedures and criteria that could be used to formulate a system for the classification of all medical devices. The recommendations of these committees were reviewed and revised by the Food and Drug Administration with the assistance of the health professions and regulated industry. These efforts resulted in the development of a classification logic system for determining one or more appropriate levels of control for any medical device. The resulting device classification system included a series of questions relating to a device's characteristics that are determinative of the appropriate classification. Those questions have been incorporated into a classification logic system which is the central element in the classification process.

The classification process itself was initiated by dividing all devices into 14 separate categories generally based on medical specialties: Orthopaedic; cardiovascular; dental; anesthesiology; obstetrical and gynecological; gastroenterology and urology; radiology; neurology; ear, nose and throat, ophthalmic; general and plastic surgery; physical medicine (physiatry); diagnostic products; and general hospital and personal use. The initial device categorization list is on public display in the office of the Hearing Clerk, Food and Drug Administration, at the address given above.

Fourteen classification panels were established corresponding with the medical specialties above and comprised of experts skilled in the use of, or experienced in the development, manufacture, or utilization of medical devices. Panel members have been selected and the panels are presently functioning in review and classification of devices that fall within their respective areas.

The 14 classification panels and their members are listed below. Of these 14 panels, the first four were established from lists of experts compiled by the Commissioner (See 38 FR 15666, July 17, 1973.) Prior to selecting members for 9 of the other 10 panels, an opportunity was provided, through notices published in the FEDERAL REGISTER, for interested persons to nominate qualified individuals with diversified expertise in such fields as clinical and administrative medicine, engineering, biological and physical sciences, and other related professions (38 FR 34353, Dec. 13, 1973; 39 FR 7191, Feb. 25, 1974, 39 FR 12288, Apr. 4, 1974). It was from these nominations that the Commissioner appointed the expert panel members to the panels. The health panel, the diagnostic products panel, received nominations from professional clinical laboratory and scientific associations and the panel members were chosen on the basis of expertise in the area of in vitro diagnostic products. Opportunity was provided for the nomination of a nonvoting consumer and industry representative to each of the 14 panels and from these the Commissioner appointed consumer and industry panel members to all 14 panels. Full-time employees of the Food and Drug Administration were not appointed as panel members.

The membership of the panels is listed below:

Orthopaedic:
Victor H. Frankel, M.D., Ph.D., Chairman.
Charles H. Epps, Jr., M.D.
Floyd R. Jorgenson, M.D.
Jacquelin Perry, M.D.
Robert V. Riechman, Ph.D.
Consumer liaison: Arthur L. Paley, M.D., Ph.D.
Industry liaison: Vacant.

Cardiovascular:
John J. Collins, Jr., M.D., Chairman.
Nina Starr Braunwald, M.D.
Clarence Dennis, M.D., Ph.D.
Jerome Liebman, M.D.
Arthur Miller, Sc.D.
Gabriel Gregoratos, M.D.
Leslie A. Geddes, Ph.D.
Consumer liaison: Margaret L. Arnold.
Industry liaison: Kenneth D. Bergen, M.D.

Dental:
John W. Stanford, Ph.D., Chairman.
Garrett V. Ridgley, D.D.S.
W. Arthur George, D.D.S.
George E. Myers, D.D.S.
Floyd A. Peyton, D.Sc.
Harold E. Boyer, D.D.S.
Frank L. Bassch.
Consumer liaison: Claire Davis.
Industry liaison: Robert H. Mercer.

Anesthesiology:
Leslie Rendell-Baker, M.D., Chairman.
James A. Meyer, M.D., D.P.H., M.P.
Eugene L. Nagel, M.D.
Stanley W. Wettimer, M.D.
Penelope Cave Smith, M.D.
Henning Pontoppidan, M.D.
John P. Swope, M.D.
Consumer liaison: Alma Ashley.
Industry liaison: Chalmers M. Goodyear.

Gastroenterology and Urology:
George R. Nagamatsu, M.D., Chairman.
Irving M. Bush, M.D.
Joseph B. Dyke, M.D.
Joyce D. Orgebuk, M.D.
W. Ray Hancock, M.D.
Victor Y. Scott, M.D.
Oscar Swenson, M.D.
Consumer liaison: J. Nathan Zeller.
Industry liaison: Lawrence E. Curtis.

Obstetrical and Gynecological:
Horace E. Thompson, M.D., Chairman.
Joel P. Borten, M.D.
Richard P. Dickey, M.D., Ph.D.
Theodore H. Frelich, D.O.

American
Dental
Association

211 East Chicago Avenue
Chicago, Illinois 60611
312/ 440-2500

ADA Ex 4

May 22, 1986

Dr. Duane E. Christian
810 North Nevada Street
Carson City, Nevada 89701

Dear Doctor Christian:

Your letter of May 14, 1986 has been received.

There appears to be confusion regarding both the role of the Council and the scope of ANSI/ADA Specification No. 1 for Alloy for Dental Amalgam. The Specification is not for dental amalgam. It is only for the alloy for dental amalgam. The amalgam does not form until the dentist mixes the alloy with mercury. Therefore, dental amalgam per se cannot be certified. We cannot certify a reaction product made by the dentist.

The requirement for review of American National Standards developed under the Accredited Standards Committee procedures of the American National Standards Institute requires that a standard or specification be reviewed once every five years. The committee responsible, in this case, ASC MD156, is required to review the document and recommend revision, reaffirmation or withdrawal. The Committee is responsible for this action, not the Council on Dental Materials, Instruments and Equipment of the Association. ASC MD156 is an independent committee and is not a Committee of the Council. The Council acts only as the administrative sponsor and provides secretarial assistance to the Committee. The Committee has representatives of 34 organizations including the Academy of General Dentistry and when ANSI/ADA Specification No. 1 was last reviewed in 1984, no member organization presented any documentation to request revision. The Committee voted unanimously to reaffirm the specification, and on February 15, 1985 the American National Standards Institute approved the reaffirmation. The specification will again be reviewed in 1990 for any revisions.

I do not know the address for Prospect Associates, who you carboned, so am enclosing a copy for Ms. Cowan of the organization for you to forward to her.

Sincerely yours,

John W. Stanford, Ph.D.
Secretary
Council on Dental Materials,
Instruments and Equipment

JWS:ph
cc: Dr. E. Neidle
Ms. L. Stovall
Dr. Michael Ziff
Dr. H. Huggins
Ms. S. Stanford

Ex. 5

[4110-03]

Title 21—Food and Drugs

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

SUBCHAPTER A—GENERAL

SUBCHAPTER H—MEDICAL DEVICES

[Docket No. 77N-0158]

Classification Procedures

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: This rule sets forth criteria and procedures for classifying devices intended for human use into classes of regulatory control sufficient to provide reasonable assurance of safety and effectiveness. The rule also explains the determination of the safety and effectiveness of devices, prescribes the procedures for the submission and review of petitions for reclassification, and defines the circumstances under which information and data associated with the classification or reclassification of devices will be released to the public. These actions are taken under the Medical Device Amendments of 1976.

EFFECTIVE DATE: August 28, 1978.

FOR FURTHER INFORMATION CONTACT:

Joseph Sheehan, Bureau of Medical Devices (HFK-70), Food and Drug Administration, Department of Health, Education, and Welfare, 8757 Georgia Avenue, Silver Spring, Md. 20910, 301-427-7114.

SUPPLEMENTARY INFORMATION: The proposal upon which this final regulation is based was published in the FEDERAL REGISTER of September 15, 1977 (42 FR 46028). Interested persons were given until November 14, 1977 to comment. Twenty-five comments were received on the proposal, presenting a wide range of issues.

This regulation essentially codifies existing procedures that have been followed in the classification process to date. Manufacturers and other interested persons have already become involved in the various aspects of the classification process described in this regulation. The agency has been urged to promulgate this regulation as quickly as possible to provide industry a more certain basis for production decisions. Although the Commissioner doubts that this procedural regulation will affect manufacturers' production decisions, the Commissioner has decided that it is in the best interest of the public and of all parties concerned that this regulation become effective August 28, 1978.

GENERAL

The Commissioner has made many minor editorial changes in the regulation for clarity.

1. Several comments stated that publication of panel recommendations and proposed regulations for the classification of devices before promulgation of the final regulation establishing classification procedures violates the basic principles of administrative rulemaking. The comments pointed out that an agency must provide public notice and an opportunity for interested parties to participate before implementation of a rule.

Section 513(c)(1) of the act requires the promulgation by regulation of the procedures to be followed by classification panels in making their reviews and recommendations. The section does not require, however, that the final classification procedures regulation precede every other step in the classification process. Moreover, this classification procedures regulation essentially codifies the procedures that the agency has been following in the classification process. Public notice of these procedures was provided in a notice published in the FEDERAL REGISTER on May 19, 1975 (40 FR 21848). Because classification panels are public advisory committees, the general procedures under which the panels operate have already been promulgated by regulation (21 CFR Part 14).

2. One comment, referring to the portion of the preamble to the proposed regulation that discussed the classification criteria (42 FR 46030), argued against consideration of such "practical matters" as the difficulty involved in enforcing general controls and the length of time required to develop performance standards. The comment stated that such considerations should be irrelevant to classification decisions, and that any inconvenience to the agency does not change the fact that adequate information may exist to allow proper classification in accordance with the statutory criteria.

The Commissioner agrees that it is improper to consider the length of time required to develop a performance standard when determining whether to classify a device into class II unless compliance with a standard is essential to provide reasonable assurance of a device's safety and effectiveness. The legislative history reveals both that Congress recognized that unavoidable time may elapse between classification of a device into class II and the development of a performance standard for the device (Sen. Rept. 94-33, p. 27), and that FDA has ample latitude to classify a device into the premarket approval category in instances in which use of the device poses public health concerns. The Commissioner believes also, however, that the degree of difficulty involved in enforcing general controls with respect to a particular device may well be a relevant consideration in determining whether general controls will provide reasonable assurance of the safety and effectiveness of the device.

3. A few comments expressed concern that the definition of "implant" in proposed § 860.3(d) would include many devices which should not be classified into class III, such as dental fillings. The comments suggested that the proposed definition be worded so as not to include such devices.

The Commissioner acknowledges the broad scope of the proposed definition, but also notes that a device which is termed an implant is not necessarily classified into class III. Sections 513 (c)(2)(C) and (d)(2)(B) of the act clearly states that an implant need not be classified into class III if such classification is not necessary to provide reasonable assurance of safety and effectiveness. The proposed definition, therefore, has been retained without change in the final regulation.

4. Several comments requested revision of the proposed definition of "life-supporting or life-sustaining device" in § 860.3(e). The comment suggested that the proposed wording is redundant and vague. The comments also stated that the proposed definition is too broad because Congress intended that only devices essential to supporting or sustaining life be considered life-supporting or life-sustaining devices for classification purposes. Some comments suggested that the words "or yields information that

be exempt from public disclosure, [illegible] of a deficiency in the petition, the petitioner is allowed a period of time in advise if the reliability of devices must be considered.

supporting of life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or of the device presents a potential unreasonable risk of illness or injury.

(d) "Implant" means a device that is placed into a surgically or naturally formed cavity of the human body. A device is regarded as an implant for the purpose of this part only if it is intended to remain implanted continuously for a period of 30 days or more, unless the Commissioner determines otherwise in order to protect human health.

"Life-supporting or life-sustaining device" means a device that is essential to, or that yields information that is essential to, the restoration or continuation of a bodily function important to the continuation of human life.

(f) "Classification questionnaire" means a specific series of questions prepared by the Commissioner for use as guidelines by classification panels preparing recommendations to the Commissioner regarding classification and by petitioners submitting petitions for reclassification. The questions relate to the safety and effectiveness characteristics of a device and the answers are designed to help the Commissioner determine the proper classification of the device.

(g) "Supplemental data sheet" means information compiled by a classification panel or submitted in a petition for reclassification, including:

(1) A summary of the reasons for the recommendation (or petition);

(2) A summary of the data upon which the recommendation (or petition) is based;

(3) An identification of the risks to health (if any) presented by the device;

(4) To the extent practicable in the case of a class II or class III device, a recommendation for the assignment of a priority for the application of the requirements of performance standards or premarket approval;

(5) In the case of a class I device, a recommendation whether the device should be exempted from any of the requirements of registration, recordkeeping and reporting, or good manufacturing practice regulations;

(6) In the case of an implant or a life-supporting or life-sustaining device for which classification in class III is not recommended, a statement of the reasons for not recommending that the device be classified in class III;

(7) Identification of any needed restrictions on the use of the device, e.g., whether the device requires special labeling, should be banned, or should be used only upon authorization of a practitioner licensed by law to administer or use such device; and

(8) Any known existing standards applicable to the device, device components, or device materials.

(h) "Classification panel" means one of the several advisory committees established by the Commissioner under section 513 of the act and part 14 of this chapter for the purpose of making recommendations to the Commissioner on the classification and reclassification of devices and for other purposes prescribed by the act or by the Commissioner.

(i) "Generic type of device" means a grouping of devices that do not differ significantly in purpose, design, materials, energy source, function, or any other feature related to safety and effectiveness, and for which similar regulatory controls are sufficient to provide reasonable assurance of safety and effectiveness.

(j) "Petition" means a submission seeking reclassification of a device in accordance with § 860.123.

§ 860.5 Confidentiality and use of data and information submitted in connection with classification and reclassification.

(a) This section governs the availability for public disclosure and the use by the Commissioner of data and information submitted to classification panels or to the Commissioner in connection with the classification or reclassification of devices under this part.

(b) In general, data and information submitted to classification panels in connection with the classification of devices under § 860.84 will be available immediately for public disclosure upon request. However, except as provided by the special rules in paragraph (c) of this section, this provision does not apply to data and information exempt from public disclosure in accordance with part 20 of this chapter. Such data and information will be available only in accordance with part 20.

(c)(1) Safety and effectiveness data submitted to classification panels or to the Commissioner in connection with the classification of a device under § 860.84, which have not been disclosed previously to the public, as described in § 20.81 of this chapter, shall be regarded as confidential if the device is classified in to class III. Because the classification of a device under § 860.84 may be reclassified only upon publication of a final regulation, all safety and effectiveness data that have not been disclosed previously are not available for public disclosure unless and until the device is classified into class I or II, in which case the procedure in paragraph (c)(2) of this section applies.

(2) Thirty days after publication of a final regulation under § 860.84 classifying a device into class I or class II, safety and effectiveness data submitted for that device that had been regarded as confidential under paragraph (c)(1) of this section will be available for public disclosure and placed on public display in the office of the Hearing Clerk, Food and Drug Administration unless, within that 30-day period, the person who submitted the data demonstrates that the data still fall within the exemption for trade secrets and confidential commercial information described in § 20.61 of this chapter. Safety and effectiveness data submitted for a device that is classified into class III by regulation in accordance with § 860.84 will remain confidential and unavailable for public disclosure so long as such data have not been disclosed to the public as described in § 20.81 of this chapter.

(3) Because device classification affects generic types of devices, in making determinations under § 860.84 concerning the initial classification of a device, the classification panels and the Commissioner may consider safety and effectiveness data developed for another device in the same generic type, regardless of whether such data are regarded currently as confidential under paragraph (c)(1) of this section.

(d)(1) The fact of its existence and the contents of a petition for reclassification filed in accordance with § 860.130 or § 860.132 are available for public disclosure at the time the petition is received by the Food and Drug Administration.

(2) The fact of the existence of a petition for reclassification filed in accordance with § 860.134 or § 860.136 is available for public disclosure at the time the petition is received by the Food and Drug Administration. The contents of such a petition are not available for public disclosure for the period of time following its receipt (not longer than 30 days) during which the petition is reviewed for any deficiencies preventing the Commissioner from making a decision on it. Once it is determined that the petition contains no deficiencies preventing the Commissioner from making a decision on it, the petition will be filed with the Hearing Clerk and its entire contents will be available for public disclosure and subject to consideration by classification panels and by the Commissioner in making a decision on the petition. If, during this 30-day period of time, the petition is found to contain deficiencies that prevent the Commissioner from making a decision on it, the petitioner will be so notified and afforded an opportunity to correct the deficiencies.

Thirty days after notice to the petitioner of deficiencies in the petition,

[redacted]

(a) Provides adequate assurance that the subjects are suitable for the purposes of the investigation and that the effective regimen (therapeutic, diagnostic, prophylactic).

will be classified by regulation into either class I (general controls), class II (performance standards), or class

Ex

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 872

[Docket No. 78N-2830]

Classification of Dental Devices; Development of General Provisions

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing general rules applicable to the classification of all dental devices. The Medical Device Amendments of 1976 require FDA to classify all medical devices intended for human use into three categories: class I, general controls; class II, performance standards; and class III, premarket approval. In the preamble to this proposal, FDA describes the development of the proposed regulations classifying individual dental devices, which are being published elsewhere in this issue of the Federal Register. The preamble also describes the activities of the Dental Device Section of the Ophthalmic; Ear, Nose, Throat; and Dental Devices Panel, an FDA advisory committee, that makes recommendations to FDA concerning the classification of dental devices.

DATES: Comments by March 2, 1981. FDA proposes that the final regulation based on this proposal become effective 30 days after the date of its publication in the Federal Register.

ADDRESS: Written comments to the office of the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Gregory Singleton, Bureau of Medical Devices (HFK-460), Food and Drug Administration, 8757 Georgia Ave., Silver Spring, MD 20910, 301-427-7536.

SUPPLEMENTARY INFORMATION:

Device Classification System

The Medical Device Amendments of 1976 (Pub. L. 94-295, hereinafter called the amendments) establish a comprehensive system for the regulation of medical devices intended for human use. One provision of the amendments, section 513 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360c) establishes three categories (classes) of devices, depending on the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories are as follows: class I, general controls; class II, performance standards; and class III, premarket approval.

Most devices are not classified under section 513 of the act until after FDA has (1) received a recommendation from a device classification panel (an FDA advisory committee); (2) published the Panel's recommendation for comment, along with a proposed regulation classifying the device; and (3) published a final regulation classifying the device. These steps must precede the classification of any device that was in commercial distribution before May 28, 1976 (the date of enactment of the amendments) and that was not previously regarded by FDA as a new drug under section 505 of the act (21 U.S.C. 355). A device that is first offered for commercial distribution after May 28, 1976, and that is substantially equivalent to a device classified under this scheme, is classified in the same class as the device to which it is substantially equivalent.

A device that FDA previously regarded as a new drug, or a newly offered device that is not substantially equivalent to a device that was in commercial distribution before the amendments, is classified by statute into class III. These two types of devices are classified into class III without any FDA rulemaking proceedings. The agency determines whether new devices are substantially equivalent to previously offered devices by means of the premarket notification procedure in section 510(k) of the act (21 U.S.C. 360(k)) and Part 807 of the regulations (21 CFR Part 807).

Related Regulations

In the Federal Register of July 28, 1978 (43 FR 32988), FDA issued final regulations describing the procedures for classifying devices intended for human use. These regulations, which were proposed in the Federal Register of September 13, 1977 (42 FR 46028), supplement the agency's regulations in Part 14 (21 CFR Part 14) governing the use of advisory committees. The agency also issued interim device classification procedures in a notice published in the Federal Register of May 19, 1975 (40 FR 21848).

Activities of Panel

Anticipating enactment of the amendments, FDA established several advisory committees to make preliminary recommendations on device classification. The Dental Device Classification Panel (the Panel) was originally chartered on October 15, 1974, as the Panel on Review of Dental Devices. FDA placed a report of the Panel's tentative classification recommendations on file with the office of the Hearing Clerk (HFA-305), Food and Drug Administration, and announced the availability of the report to the public by notice published in the Federal Register of June 25, 1976 (41 FR 26245). On August 9, 1976, the Panel and other preamendments device classification panels were rechartered to reflect their new responsibilities under the amendments. The agency directed each panel to reconsider its preamendments classification recommendations in light of the new requirements. In 1976 and 1977, the Panel reviewed all devices that FDA had referred to it to make certain that its recommendations were in accord with the amendments. Throughout the Panel's deliberations, interested persons were given an opportunity to present their views, data, and other information concerning the classification of dental devices. The Panel also invited experts to testify and sought information on many devices from the published literature.

In October 1977, the Panel submitted to FDA a preliminary report of its recommendations. The report included a roster of current and former Panel members and consultants and listed all meeting dates. The agency placed a copy of the report in the office of the Hearing Clerk (HFA-305), Food and Drug Administration, and announced its availability to the public by notice published in the Federal Register of November 29, 1977 (42 FR 60792). Also available in the office of the Hearing Clerk are summary minutes from all Panel meetings, verbatim transcripts of meetings held after May 28, 1976 (the date of enactment of the amendments), and all references cited in individual dental device proposed classification regulations.

On April 28, 1978, the agency terminated all of the device classification panels, and then reestablished them with new names and with a new structure. FDA published notices of these changes in the Federal Register of May 19, 1978 (43 FR 21666, and 21668) and May 26, 1978 (43 FR 22672 and 22673). The Dental Device Classification Panel was terminated, and its functions are now conducted by the Dental Device Section of the Ophthalmic; Ear, Nose, Throat; and Dental Devices Panel.

Relationship Between the Device Names in the Device Registration and Listing Codes and the Device Names in Classification Regulations

Some manufacturers have become accustomed to identifying a device by

Panel's recommended priority ("high," "medium," or "low") for application of premarket approval requirements to that device. As explained below in the section of this notice concerning "Priorities for Class II and III Devices," the agency is not, however, proposing the establishment of FDA priorities at this time.

5. *Risks to health.* In identifying the risks to health presented by dental devices, the Panel recognized that few devices are completely free of risk. The Panel listed the risks it considered most significant, especially those that are unique to the individual device. In some cases, FDA has identified risks to health presented by a device in addition to

of the agency's letter to members of the Section is on file with the Hearing Clerk, at the address noted above (Ref. 1).

FDA cautions that the final classification of a device may differ from the proposal. Factors that may cause such a change include comments, the agency's reconsideration of existing data and information, and the agency's

FDA has determined that no device that is labeled or otherwise represented as sterile will be exempted from the device GMP regulation. A sterile device must be subject to the entire GMP regulation to ensure that manufacturers adequately reduce the bioburden (number of microorganisms) on the device and its components during the manufacturing process. This reduction is accomplished through adherence to a comprehensive quality assurance program as is required by the GMP regulation, with adequate environmental controls, trained personnel, appropriate maintenance and calibration of sterilization equipment, recordkeeping concerning lot sterility, strict packaging and labeling controls, and other quality assurance measures.

The agency also has determined that no exemption from the device GMP regulation will extend to § 820.180, with respect to general requirements concerning records, or § 820.198, with respect to complaint files. The agency believes that granting exemptions from these sections would not be in the public interest and that compliance with these sections is not unduly burdensome for device manufacturers. To ensure that device manufacturers have adequate systems for complaint investigation and followup, all manufacturers are required to comply with the complaint file requirements. All device manufacturers also are required to comply with the general requirements concerning records to ensure that FDA has access to complaint files, can investigate device-related injury reports and complaints about product defects, can determine whether the manufacturer's corrective actions are adequate, and can determine whether the exemption from other sections of the GMP regulation is still appropriate.

In general, FDA has not initiated proposals to exempt manufacturers of devices from requirements under section 510 or 520(f) of the act, but has acted on the basis of exemption recommendations of the device classification panels. However, FDA has proposed occasionally to exempt manufacturers of certain devices classified into class I or class II from the requirements of certain sections of the GMP regulation, according to the above exemption criteria. Manufacturers and other interested persons may submit comments on the appropriateness of the proposed exemptions of manufacturers of devices, whether the exemptions are proposed in response to recommendations of the panels or on the agency's initiative. Comments requesting additional exemptions should be supported by information showing that the exemption of manufacturers of a device from the premarket notification requirement or the GMP regulation is consistent with the criteria discussed above.

Guidelines for Preparing Petitions Requesting Exemption or Variance From the Device GMP Regulation for Devices Classified Into Class I or Class II

FDA has prepared guidelines on the procedures that should be followed by persons who wish to submit petitions for exemption or variance from the device GMP regulation. These petitions may be submitted in accordance with provisions of section 520(f)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360j(f)(2)). The agency announced the availability of the guidelines in a notice published in the **Federal Register** of January 18, 1980 (45 FR 3671).

List of Dental Devices

The following is a list of dental devices that FDA is proposing to classify, the section and subpart of Part 872 in the Code of Federal Regulations under which the regulation classifying the device will be codified, the docket number of the proposed classification regulation, and the proposed classification of each device.

Section	Device	Docket No.	Class
Subpart B—Dental Diagnostic Devices			
872.1500	Gingival fluid measurer	78N-2831	I
872.1720	Pulp tester	78N-2834	II
872.1730	Electrode gel for pulp tester	78N-2835	II
872.1800	Extraoral source X-ray system	78N-2836	II
872.1810	Intraoral source X-ray system	78N-2837	II
872.1820	Dental X-ray exposure alignment device	78N-2838	II
872.1830	Cephalometer	78N-2839	II
872.1840	Dental X-ray position indicating device	78N-2840	II
872.1850	Lead-lined position indicator	78N-2841	II
872.1905	Dental X-ray film holder	78N-2842	II
Subpart D—Dental Prosthetic Devices			
872.3050	Amalgam alloy	78N-2843	II
872.3060	Gold-based alloy for clinical use	78N-2844	II
872.3070	Precious metal alloy for clinical use	78N-2845	II
872.3080	Mercury and alloy dispenser	78N-2846	II
872.3100	AC-powered dental amalgamator	78N-2847	II
872.3110	Dental amalgam capsule	78N-2848	II
872.3130	Preformed anchor	78N-2849	II
872.3140	Resin applicator	78N-3024	I
872.3150	Articulator	78N-2850	I
872.3165	Precision attachment	78N-2851	II
872.3175	Performed bar	78N-2852	II
872.3200	Resin tooth bonding agent	78N-2853	I
872.3220	Facebow	78N-2854	I
872.3240	Dental bur	78N-2855	II
872.3250	Calcium hydroxide cavity liner	78N-2856	II
872.3260	Cavity varnish	78N-2857	II
872.3275	Dental cement	78N-2858	II
872.3285	Preformed clasp	78N-2859	II
872.3294	Preformed wire clasp	78N-2860	II
872.3300	Hydrophilic resin coating for dentures	78N-2861	II
872.3310	Casting material for resin fillings	78N-2862	II
872.3330	Preformed crown	78N-2863	II
872.3350	Gold and stainless steel cusp	78N-2864	II
872.3360	Preformed cusp	78N-2865	II
872.3400	Acacia and karaya with sodium borate denture adhesive	78N-2866	III
872.3410	Carboxymethylcellulose sodium (40 to 100 percent) denture adhesive.	78N-2867	II
872.3420	Carboxymethylcellulose sodium and cationic polyacrylamide polymer denture adhesive.	78N-2868	III
872.3430	Carboxymethylcellulose sodium (22 percent) and ethylene oxide homopolymer (13 percent) denture adhesive.	78N-2869	II
872.3440	Carboxymethylcellulose sodium (18 percent) and ethylene oxide homopolymer (21 percent) denture adhesive.	78N-2870	II
872.3450	Karaya denture adhesive	78N-2871	II
872.3460	Karaya and ethylene oxide homopolymer denture adhesive	78N-2872	II
872.3470	Karaya with sodium borate denture adhesive	78N-2873	III
872.3480	Polyacrylamide polymer (modified cationic) denture adhesive	78N-2874	III
872.3490	Polyvinylmethylether-maleic acid calcium-sodium double salt denture adhesive	78N-2875	II

Section	Device	Docket No.	Class
Subpart B—Dental Diagnostic Devices—Continued			
872.6510	Preformed orthodontic spacer/retainer	78N-2961	II
872.6520	Orthodontic pliers	78N-2962	I
872.6525	Preformed tooth positio	78N-3026	II
872.6530	Orthodontic expansion	78N-2963	II
872.6540	Orthodontic spring	78N-2964	II

Section	Device	Docket No.	Class
Subpart D—Dental Prosthetic Devices—Continued			
872.3500	Polyvinylmethylether maleic anhydride (PVM-MA), acid copolymer and carboxymethyl cellulose sodium (NACMC) denture adhesive.	78N-2876	III
872.3510	Polyvinyl methylether maleic acid calcium-sodium double salt and carboxymethylcellulose sodium denture adhesive.	78N-2877	II
872.3520	OTC denture cleanser	78N-2878	II
872.3530	Mechanical denture cleaner	78N-2879	II
872.3540	Over-the-counter (OTC) denture cushion	78N-2880	III
872.3550	Over-the-counter (OTC) denture pad	78N-2881	III
872.3560	Over-the-counter (OTC) denture reliner	78N-2882	III
872.3570	Over-the-counter (OTC) denture repair kit	78N-2883	III
872.3580	Preformed gold denture tooth	78N-2884	II
872.3590	Preformed plastic denture tooth	78N-2885	II
872.3600	Partially fabricated denture kit	78N-2886	III
872.3640	Endosseous implant	78N-2887	III
872.3645	Titanium subperiosteal implant material	78N-2888	II
872.3650	Cobalt chrome molybdenum subperiosteal implant material	78N-2889	II
872.3660	Impression material	78N-2890	II
872.3670	Resin impression tray material	78N-2891	I
872.3680	Polytetrafluoroethylene (PTFE) wrought carbon material	78N-2892	II
872.3690	Tooth shade resin material	78N-2893	II
872.3700	Dental mercury	78N-2894	II
872.3710	Base metal alloy	78N-2895	II
872.3730	Pantograph	78N-2897	I
872.3740	Retentive and splinging pin	78N-2898	III
872.3760	Bracket adhesive resin and tooth conditioner	78N-2899	III
872.3780	Denture relining, repairing, or rebasing resin	78N-2900	II
872.3785	Pit and fissure sealant and conditioner	78N-2901	II
872.3790	Temporary crown and bridge resin	78N-2902	II
872.3810	Root canal post	78N-2904	II
872.3820	Root canal filling resin	78N-2905	II
872.3830	Endodontic paper point	78N-2906	II
872.3840	Endodontic silver point	78N-2907	II
872.3850	Gutta percha	78N-2908	II
872.3860	Endodontic stabilizing splint	78N-2909	II
872.3900	Posterior artificial teeth with metal insert	78N-2910	II
872.3910	Backing and facing for artificial teeth	78N-2911	II
872.3920	Porcelain teeth	78N-2912	II
872.3960	Zinc oxide eugenol	78N-2913	II
Subpart E—Dental Surgical Devices			
872.4040	Endodontic broach	78N-2927	II
872.4075	Dental wax carver	78N-2914	I
872.4120	Manual bone drill and wire driver	78N-2916	II
872.4130	Intraoral dental drill	78N-2916	II
872.4140	Powered bone drill	78N-2917	II
872.4150	Endodontic pulp canal file	78N-3026	II
872.4200	Air-powered dental handpiece	78N-2918	II
872.4220	Belt-driven dental handpiece	78N-2919	II
872.4240	Rotary bone-cutting handpiece	78N-2920	II
872.4260	Contra-angle handpiece attachment	78N-2921	II
872.4280	Direct drive handpiece	78N-2922	II
872.4300	Foot continuity for handpiece	78N-2923	I
872.4320	Water-powered handpiece	78N-2924	II
872.4465	Gas-powered jet injector	78N-2925	II
872.4475	Spring-powered jet injector	78N-2926	II
872.4500	Hand instrument for calculus removal	78N-2927	II
872.4520	Dental depth gauge instrument	78N-2928	I
872.4525	Dental diamond instrument	78N-2929	II
872.4555	Plastic dental filling instrument	78N-2930	I
872.4565	Dental hand instruments	78N-2931	I
872.4575	Dental instrument handle	78N-2932	I
872.4600	Intraoral ligature and wire lock	78N-2933	II
872.4620	Fiber-optic dental light	78N-2934	II
872.4630	Dental operating light	78N-2936	II
872.4640	Surgical headlight	78N-2936	II
872.4730	Dental piercing needle	78N-2937	II
872.4760	Bone plate	78N-2938	II
872.4820	AC-powered bone saw	78N-2941	II
872.4840	Rotary saw	78N-2942	II
872.4850	Ultrasonic scaler	78N-2943	II
872.4875	Surgical tissue scissors	78N-2945	II
872.4880	Intraosseous fixation screw	78N-2946	II
872.4930	Dental hydrosurgical unit and accessories	78N-2947	II
872.4950	Intraosseous fixation wire	78N-2948	II
Subpart F—Dental Therapeutic Devices			
872.5400	Orthodontic elastic band	78N-2950	II
872.5410	Orthodontic fabricated band	78N-2951	II
872.5420	Orthodontic band driver	78N-2952	I
872.5430	Orthodontic band material	78N-2953	II
872.5440	Orthodontic band pusher	78N-2954	I
872.5450	Orthodontic band seater	78N-2955	I
872.5460	Orthodontic metal bracket	78N-2956	II
872.5470	Orthodontic plastic bracket	78N-2957	II
872.5480	Orthodontic bracket aligner	78N-2958	I
872.5490	Orthodontic wire clamp	78N-2959	II
872.5500	Expansion orthodontic headgear	78N-2960	II

Luer-lock drug syringes—General Medical
Tongue depressor—General Medical
Gauze sponge—Surgical and Rehabilitation
Surgical knife—Surgical and Rehabilitation
Dental suture—Surgical and Rehabilitation

Neurological Device Section—November 28, 1978, 43 FR 54040-54732 (proposals); September 4, 1979, 44 FR 51720-51778 (final regulations)

Consultant and Rehabilitation Devices Panel

that Panel recommendation, classifying the dry heat sterilizer into class II.

2. The Ophthalmic, Ear, Nose, Throat, and Dental Devices Panel recommends that both the air or water bulb syringe and the irrigation syringe be classified

Section	Device	Docket No.	Class
Subpart B—Dental Diagnostic Devices—Continued			
872.5810	Preformed orthodontic space maintainer	78N-2961	II
872.5830	Orthodontic pliers	78N-2962	I
872.5835	Preformed tooth positioner	78N-2978	II
872.5840	Orthodontic expansion screw retainer	78N-2963	II
872.5840	Orthodontic spring	78N-2964	II
872.5845	Teething ring	78N-2965	I, II
872.5850	Orthodontic tube	78N-2966	II
872.5870	Orthodontic ligature tucking instrument	78N-2967	I
872.5940	Orthodontic wire	78N-2968	II
Subpart C—Dental Miscellaneous Devices			
872.6010	Abrasive disk	78N-2969	II
872.6020	Abrasive point	78N-2970	II
872.6030	Oral cavity abrasive polishing agent	78N-2971	II
872.6050	Polishing agent strip	78N-2972	I
872.6040	Polishing wheel	78N-2973	I, II
872.6060	Paper saliva absorber	78N-2974	I
872.6070	Ultraviolet activator for polymerization	78N-2975	II
872.6080	Airbrush	78N-2976	III
872.6100	Anesthetic warmer	78N-2977	I
872.6140	Articulation paper	78N-2979	I
872.6200	Base plate shellac	78N-2979	II
872.6250	Dental chair with operative unit	78N-2980	II
872.6260	Dental chair without operative unit	78N-2981	II
872.6280	Cotton rod	78N-2982	I
872.6290	Prophylaxis cup	78N-2983	I
872.6300	Rubber dam	78N-2984	I
872.6310	Rubber dam clamp	78N-2985	I
872.6320	Rubber dam frame	78N-2986	I
872.6350	Ultraviolet detector	78N-2987	II
872.6370	Oral cavity evacuator	78N-2988	I
872.6760	Dental floss	78N-2989	I
872.6400	Forceps for articulation paper	78N-2990	I
872.6410	Forceps for dental dressing	78N-2991	I
872.6420	Forceps for a rubber dam clamp	78N-2992	I
872.6460	Guard for an abrasive disk	78N-2993	I
872.6475	Heat source for bleaching teeth	78N-2994	II
872.6510	Oral irrigation unit	78N-2995	II
872.6550	Dental matrix band	78N-2997	I
872.6560	Matrix retainer	78N-2998	I
872.6570	Impression tube	78N-2999	I
872.6600	Mouth mirror	78N-3000	I
872.6620	Saliva ejector mouthpiece	78N-3001	I
872.6640	Dental operative unit	78N-3002	II
872.6645	Suction operative unit	78N-3003	II
872.6650	Massaging pick	78N-3004	II
872.04		78N-30	I
872.6660	Porcelain powder for clinical use	78N-3005	II
872.6670	Silicate protector	78N-3006	I
872.6680	Dental retractor (all types)	78N-3007	II
872.6690	Dental retractor accessories	78N-3008	II
872.6710	Boiling water sterilizer	78N-3009	II
872.6730	Endodontic dry heat sterilizer	78N-3011	III
872.6760	Air or water syringe unit	78N-3012	I
872.6770	Cartridge syringe	78N-3014	II
872.6800	Periodontic or endodontic irrigating syringe	78N-3016	I
872.6810	Reservoir or impression material syringe	78N-3017	I
872.6850	Rubber tip for oral hygiene	78N-3018	I
872.6855	Manual toothbrush	78N-3019	I
872.6856	Powered toothbrush	78N-3020	II
872.6870	Disposable fluoride tray	78N-3021	I
872.6880	Preformed impression tray	78N-3022	I
872.6890	Intraoral dental wax	78N-3023	II

Devices Considered by Two or More Panels

The Dental Device Section of the Ophthalmic; Ear, Nose, Throat; and Dental Devices Panel and the other panels listed below made classification recommendations concerning the following devices:

Device—Other Panels

X-ray film cassette—Obstetrics-Gynecology and Radiologic
Extra oral X-ray dental film—Obstetrics-Gynecology and Radiologic
Intra oral X-ray dental film—Obstetrics-Gynecology and Radiologic
Intensifying radiographic screen—Obstetrics-Gynecology and Radiologic
Automatic radiographic film processor—Obstetrics-Gynecology and Radiologic
Leaded apron—Obstetrics-Gynecology and Radiologic
Leaded operator radiation protector—Obstetrics-Gynecology and Radiologic
Anesthesia flowmeter—Respiratory and Nervous System
Compressed gas cylinder and valve—Respiratory and Nervous System
Analgesia/anesthesia gas machine—Respiratory and Nervous System
Resuscitation and emergency oxygen unit—Respiratory and Nervous System
Cotton applicator—General Medical
Autoclave—General Medical
Ethylene oxide gas sterilizer—General Medical

U.S.C. 360c, 371(a))), and under authority delegated to him (21 CFR 5.1), the Commissioner of Food and Drugs proposes that Chapter I of Title 21 of the code of Federal Regulations be amended by adding new Part 872, Subpart A, to read as follows:

PART 872—DENTAL DEVICES

with the Hearing Clerk, Food and Drug Administration.

Dated: December 16, 1980.

William F. Randolph,
Acting Associate Commissioner for Regulatory Affairs.

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BILLING CODE 4110-03-M

2. Recommended classification: Class I (general controls). The Panel recommends that this device be exempt from premarket notification under section 510(k) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360(k)), records and reports requirements under section 519 of the act (21 U.S.C. 360i), and the good manufacturing practice regulation under section 520(f) of the act

development of the proposed regulation. The Dental Device Classification Panel, an FDA advisory committee, made the following recommendation regarding the classification of dental X-ray film holders:

1. Identification: A dental X-ray film holder is a device used to position and to hold X-ray film inside the mouth.

2. Recommended classification: Class I (general controls). The Panel recommends that this device be exempt from premarket notification under section 510(k) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360(k)), records and reports requirements under section 519 of the act (21 U.S.C. 360i), and the good manufacturing practice regulation under section 520(f) of the act (21 U.S.C. 360(f)).

3. Summary of reasons for recommendation: The Panel recommends that dental X-ray film holders be classified into class I because the Panel believes that general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device. This device has been used in dentistry for many years. The materials used in the device that contact the body have known and acceptable properties. The Panel believes that manufacturers should not be required to comply with premarket notification notification procedures, records and reports requirements, and the good manufacturing practice regulation because the Panel believes that defects in this device are readily apparent to the user.

4. Summary of data on which the recommendation is based: The Panel based its recommendation on the Panel members' personal knowledge of, and clinical experience with, dental X-ray film holders in the practice of dentistry.

5. Risks to health: Infection: If the materials used in the device cannot be properly sterilized, a patient may contract an infection.

Proposed Classification

FDA disagrees with the Panel recommendation and is proposing that dental X-ray film holders be classified into class II (performance standards). This decision is based on the knowledge that a single dental X-ray film holder may be used for many patients and has the potential for transmitting microorganisms between patients. Therefore, these devices must be constructed of materials that can be properly sterilized. The agency believes that a performance standard is necessary for this device because general controls alone are insufficient to control the risks to health presented by the device. A performance standard would provide reasonable assurance of the safety and effectiveness of the device. The agency also believes that there is sufficient information to establish a performance standard for this device.

Because the agency has determined that dental X-ray film holders should be classified into class II rather than class I, the agency is not required to publish a regulation adopting or rejecting the Panel's recommendation that this device be exempt from premarket notification procedures under section 510(k), records and reports requirements under section 519, and the good manufacturing practice regulation under section 520(f) of the act.

On April 28, 1976, the agency terminated all of the device classification panels and reestablished them with the same functions, but with new names and a new structure. FDA published notices of these changes in the Federal Register of May 19, 1976 (43 FR 21660, 21667, and 21668) and May 20, 1976 (43 FR 22072 and 22073). This proposed classification regulation identifies each device panel by the former name. Further information regarding the device advisory committees and list of their new names may be found in the preamble to the general provisions, published elsewhere in this issue of the **Federal Register**.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 513, 701(a), 52 Stat. 1055, 90 Stat. 540–540 (21 U.S.C. 360c, 371(a))) and under authority delegated to him (21 CFR 5.1), the Commissioner of Food and Drugs proposes to amend Part 872 in Subpart B by adding new § 872.1905, to read as follows:

§ 872.1905 X-ray film holder.

(a) *Identification.* A dental X-ray film holder is a device used to position and to hold X-ray film inside the mouth.

(b) *Classification.* Class II (performance standards).

Interested persons may, on or before March 2, 1981, submit to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Four copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the Hearing Clerk docket number found in brackets in the heading of this document. Received comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

Dated: November 19, 1980.

William F. Randolph,
Acting Associate Commissioner for Regulatory Affairs.

[FR Doc. 80-39024 Filed 12-29-80; 8:45 am]
BILLING CODE 4110-03-M

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21 CFR Part 872

[Docket No. 78N-2043]

Medical Devices; Classification of Amalgam Alloys

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing for public comment a proposed regulation classifying amalgam alloys into class II (performance standards). FDA is also publishing the recommendation of the Dental Device Classification Panel that the device be classified into class II. The effect of classifying a device into class II is to provide for the future development of one or more performance standards to assure the safety and effectiveness of the device. After considering public comments, FDA will issue a final regulation classifying the device. These actions are being taken under the Medical Device Amendments of 1976.

DATES: Comments by March 2, 1981. FDA proposed that the final regulation based on this proposal become effective 30 days after the date of its publication in the **Federal Register**.

ADDRESS: Written comments to the office of the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Gregory Singleton, Bureau of Medical Devices (HFK-460), Food and Drug Administration, 8757 Georgia Ave., Silver Spring, MD 20910, 301–427–7536.

SUPPLEMENTARY INFORMATION:

Panel Recommendation

A proposal elsewhere in this issue of the **Federal Register** provides background information concerning the development of the proposed regulation. The Dental Device Classification Panel, an FDA advisory committee, made the following recommendation regarding the classification of amalgam alloys:

1. Identification: An amalgam alloy is a device that consists of a metallic substance that is mixed with mercury to form filling material for dental caries.

2. Recommended classification: Class II (performance standards). The Panel recommends that establishing a

Proposed Classification

FDA agrees with the Panel recommendation and is proposing that gold-based alloy for clinical use be classified into class II (performance standards). The agency believes that

9 a.m. and 4 p.m., Monday through Friday.

Dated: November 19, 1980.

William F. Randolph,
Acting Associate Commissioner for Regulatory Affairs.

contain smaller quantities of other metals, such as copper, gold, and platinum. It is used to fabricate dental appliances such as crowns and bridges.

2. Recommended classification: Class II (performance standards). The Panel

performance standard for this device be a medium priority.

3. Summary of reasons for recommendation: The Panel recommends that amalgam alloys be classified into class II because materials used in the device that contact the body should meet a generally accepted and satisfactory level of tissue compatibility. The Panel believes that general controls alone would not provide sufficient control over this characteristic. The Panel believes that a performance standard would provide reasonable assurance of the safety and effectiveness of the device and that there is sufficient information to establish a performance standard.

4. Summary of data on which the recommendation is based: The Panel based its recommendation on the Panel members' personal knowledge of, and clinical experience with, the device in the practice of dentistry.

5. Risks to health: (a) Adverse gastric or respiratory response: Ingestion of the powdered alloy or the mixed amalgam may be harmful to the patient's digestive or respiratory tract. (b) Adverse tissue reaction: If the materials in the device are not biocompatible, the patient may have an adverse tissue reaction.

Proposed Classification

FDA agrees with the Panel recommendation and is proposing that amalgam alloys be classified into class II (performance standards). The agency believes that a performance standard is necessary for this device because general controls alone are insufficient to control the risks to health presented by the advice. A performance standard would provide reasonable assurances of the safety and effectiveness of the device. The agency also believes that there is sufficient information to establish a performance standard for this device.

On April 28, 1976, the agency terminated all of the device classification panels and reestablished them with the same functions, but with new names and a new structure. FDA published notices of these changes in the **Federal Register** of May 19, 1976 (43 FR 21660, 21668) and May 28, 1976 (43 FR 22672 and 22673). This proposed classification regulation identifies each device panel by the former name. Further information regarding the device advisory committees and list of their new names may be found in the preamble to the general provisions, published elsewhere in this issue of the **Federal Register.**

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 513, 701(a), 52 Stat. 1055, 90 Stat. 540–546 (21 U.S.C. 360c, 371(a))) and under authority delegated to him (21 CFR 5.1), the Commissioner of Food and Drugs proposes to amend Part 872 by adding new Subpart C, which is reserved, and adding new Subpart D and § 872.3050, to read as follows:

Subpart C—Reserved

Subpart D—Prosthetic Devices

§ 872.305 Amalgam alloy.

(a) *Identification.* An amalgam alloy is a device that consists of a metallic substance that is to be mixed with mercury to form filling material for dental caries.

(b) *Classification.* Class II (performance standards).

Interested persons may, on or before March 2, 1981, submit to the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Four copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the Hearing Clerk docket number found in brackets in the heading of this document. Received comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

Dated: November 19, 1980.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

[FR Doc. 80-39653 Filed 12-29-80; 8:45 am]

BILLING CODE 4110-03-M

21 CFR Part 872

[Docket No. 78N-2844]

Medical Devices; Classification of Gold-Based Alloy for Clinical Use

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing for public comment a proposed regulation classifying gold-based alloy for clinical use into class II (performance standards). FDA is also publishing the recommendation of the Dental Device Classification Panel that the device be classified into class II. The effect of classifying a device into class II is to provide for the future development of one or more performance standards to assure the safety and effectiveness of the device. After considering public comments, FDA will issue a final regulation classifying the device. These actions are being taken under the Medical Device Amendments of 1976.

DATES: Comments by March 2, 1981. FDA proposes that the final regulation based on this proposal become effective 30 days after the date of its publication in the **Federal Register.**

ADDRESS: Written comments to the office of the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Gregory Singleton, Bureau of Medical Devices (HFK–400), Food and Drug Administration, 8757 Georgia Ave., Silver Spring, MD 20910, 301–427–7536.

SUPPLEMENTARY INFORMATION:

Panel Recommendation

A proposal elsewhere in this issue of the **Federal Register** provides background information concerning the development of the proposed regulation. The Dental Device Classification Panel, an FDA advisory committee, made the following recommendation regarding the classification of gold-based alloy for clinical use:

1. Identification: A gold-based alloy for clinical use is a mixture of metals, the major component of which is gold. It may also contain smaller quantities of silver, copper, platinum, or palladium. It is used to fabricate custom-made dental appliances, such as crowns and bridges.

2. Recommended classification: Class II (performance standards). The Panel recommends that establishing a performance standard for gold-based alloy for clinical use be a low priority.

3. Summary of reasons for recommendation: The Panel recommends that gold-based alloy for clinical use be classified into class II because the materials used in the device that contact the body should meet a generally accepted and satisfactory level of tissue compatibility. The Panel believes that a performance standard would provide reasonable assurance of the safety and effectiveness of the device and that there is sufficient information to establish a performance standard.

4. Summary of data on which the recommendation is based: The Panel based its recommendation on the Panel members' personal knowledge of, and clinical experience with, the device in the practice of dentistry.

5. Risks to health: Adverse tissue reaction: If materials used in the device are not biocompatible, the patient may have an adverse tissue reaction.

general provisions, published elsewhere in this issue of the **Federal Register.**

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 513,

safety and effectiveness of the device. The effect of classifying a device into class I is to require that the device meet only the general controls applicable to

believes that manufacturers of this device should not be required to comply with premarket notification procedures, records and reports requirements, and the good manufacturing practice

general provisions, published elsewhere in this issue of the Federal Register.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 513, 701(a), 52 Stat. 1055, 59 Stat. 540–546 (21 U.S.C. 360c, 371(a))) and under authority delegated to him (21 CFR 5.1), the Commissioner of Food and Drugs proposes to amend Part 872 in Subpart D by adding new § 872.3070, to read as follows:

§ 872.3070 Precious metal alloy for clinical use.

(a) *Identification.* A precious metal alloy for clinical use is a mixture of metals, the major components of which are silver and palladium. It may also contain smaller quantities of other metals, such as copper, gold, and platinum. It is used to fabricate dental appliances such as crowns and bridges.

(b) *Classification.* Class II (performance standards).

Interested persons may, on or before March 2, 1981, submit to the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Four copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the Hearing Clerk docket number found in brackets in the heading of this document. Received comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

Dated: November 19, 1980.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

FR Doc. 80-38827 Filed 12-29-80; 8:45 am]

BILLING CODE 4110-03-M

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21 CFR Part 872

[Docket No. 78N-2346]

Medical Devices; Classification of Mercury and Alloy Dispensers

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing for public comment a proposed regulation classifying mercury and alloy dispensers into class II (performance standards). FDA is also publishing the recommendation of the Dental Device Classification Panel that the device be classified into class I (general controls). The effect of classifying a device into class II is to provide for the future development of one or more performance standards to assure the safety and effectiveness of the device. The effect of classifying a device into class I is to require that the device meet only the general controls applicable to all devices. After considering public comments, FDA will issue a final regulation classifying the device. These actions are being taken under the Medical Device Amendments of 1976.

DATES: Comments by March 2, 1981. FDA proposes that the final regulation based on this proposal become effective 30 days after the date of its publication in the Federal Register.

ADDRESS: Written comments to the office of the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Gregory Singleton, Bureau of Medical Devices (HFK–460), Food and Drug Administration, 8757 Georgia Ave., Silver Spring, MD 20910, 301–427–7538.

SUPPLEMENTARY INFORMATION:

Panel Recommendation

A proposal elsewhere in this issue of the Federal Register provides background information concerning the development of the proposed regulation. The Dental Device Classification Panel, an FDA advisory committee, made the following recommendation regarding the classification of mercury and alloy dispensers:

1. Identification: A mercury and alloy dispenser is a device used to measure and dispense a predetermined amount of dental mercury in droplet form and a premeasured amount of alloy pellets. The device uses a spring-activated valve to deliver the materials into a mixing capsule.

2. Recommended classification: Class I (general controls). The Panel recommends that this device be exempt from premarket notification procedures under section 510(k) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360(k)), records and reports requirements under section 519 of the act (21 U.S.C. 360i), and the good manufacturing practice regulation under section 520(f) of the act (21 U.S.C. 360j(f)).

3. Summary of reasons for recommendation: The Panel recommends that mercury and alloy dispensers be classified into class I because the Panel believes that general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device. This device has been used in dentistry for many years. The materials used in the device that contact the body have known and acceptable properties. The Panel believes that manufacturers of this device should not be required to comply with premarket notification procedures, records and reports requirements, and the good manufacturing practice regulation because this is a simple device that presents no undue risks to health when used in a normal manner and for the purpose recommended.

4. Summary of data on which the recommendation is based: The Panel based its recommendation on the Panel members' personal knowledge of, and clinical experience with, mercury and alloy dispensers in the practice of dentistry.

5. Risks to health: None identified.

Proposed Classification

FDA disagrees with the Panel recommendation and is proposing that mercury and alloy dispensers be classified into class II (performance standards). Mercury is toxic to humans. For many years, spillage or leakage of mercury has been considered a hazard to dental patients, the dentist, and staff workers. Leakage of mercury from the device may cause acute or chronic mercury toxicity through inhalation of mercury vapors. Failure of the device to dispense an accurate amount of mercury could affect the physical properties of the carle filling material, resulting in early failure of the filling. The agency believes that a performance standard is necessary for this device because general controls alone are insufficient to control the risks to health presented by the device. A performance standard would provide reasonable assurance of the safety and effectiveness of the device. The agency also believes that there is sufficient information to establish a performance standard for this device.

Because the agency has determined that mercury and alloy dispensers should be classified into class II rather than class I, the agency is not required to publish a regulation adopting or rejecting the Panel recommendation that this device be exempt from premarket notification procedures under section 510(k), records and reports requirements under section 519, and the good manufacturing practice regulation under section 520(f) of the act.

On April 28, 1978, the agency terminated all of the device classification panels and reestablished them with the same functions, but with new names and a new structure. FDA published notices of these changes in the Federal Register of May 19, 1978 (43 FR 21666, 21667, and 21668) and May 26, 1978 (43 FR 22672 and 22673). This proposed classification regulation identifies each device panel by the

Clerk (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Four copies of any comments are to be

Panel Recommendation

A proposal elsewhere in this issue of the Federal Register provides background information concerning the development of the proposed regulation.

standard is necessary to assure that dental amalgam capsules can safely be used to perform this mixing process without exposing patients and dental care workers to mercury vapors and because general controls alone are

Clerk (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Four copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the Hearing Clerk docket number found in brackets in the heading of this document. Received comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

Dated: November 19, 1980

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

[FR Doc. 80-38629 Filed 12-29-80; 8:45 am]

BILLING CODE 4110-03-M

21 CFR Part 872

[Docket No. 78N-2848]

Medical Devices; Classification of Dental Amalgam Capsules

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing for public comment a proposed regulation classifying dental amalgam capsules into class II (performance standards). FDA is also publishing the recommendation of the Dental Device Classification Panel that the device be classified into class I (general controls). The effect of classifying a device into class II is to provide for the future development of one or more performance standards to assure the safety and effectiveness of the device. The effect of classifying a device into class I is to require that the device meet only the general controls applicable to all devices. After considering public comments, FDA will issue a final regulation classifying the device. These actions are being taken under the Medical Device Amendments of 1976.

DATES: Comments by March 2, 1981. FDA proposes that the final regulation based on this proposal become 78-2418 effective 30 days after the date of its publication in the Federal Register.

ADDRESS: Written comments to the office of the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Gregory Singleton, Bureau of Medical Devices (HFK-460), Food and Drug Administration, 8757 Georgia Ave., Silver Spring, MD 20910, 301-427-7536

SUPPLEMENTARY INFORMATION:

Panel Recommendation

A proposal elsewhere in this issue of the Federal Register provides background information concerning the development of the proposed regulation. The Dental Device Classification Panel, an FDA advisory committee, made the following recommendation regarding the classification of dental amalgam capsules:

1. Identification: A dental amalgam capsule is a container device in which silver alloy is mixed with mercury to form dental amalgam.

2. Recommended classification: Class I (general controls). The Panel recommends that this device be exempt from records and reports requirements under section 519 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360i) and the good manufacturing practice regulation under section 520(f) of the act (21 U.S.C. 360j(f)).

3. Summary of reasons for recommendation: The Panel recommends that dental amalgam capsules be classified into class I because the Panel believes that general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device. This device has been used in dentistry for many years. The materials used in the device that contact the body have known and acceptable properties. The Panel believes that manufacturers should not be required to comply with records and reports requirements and the good manufacturing practice regulation because it is a simple device that presents no undue risks to health when used in a normal manner and for the purpose recommended.

4. Summary of data on which the recommendation is based: The Panel based its recommendation on the Panel members' personal knowledge of, and clinical experience with, dental amalgam capsules in the practice of dentistry.

5. Risks to health: None identified.

Proposed Classification

FDA disagrees with the Panel recommendation and is proposing that dental amalgam capsules be classified into class II (performance standards). Dental amalgam capsules are used to mix amalgam materials, one component of which is mercury. Mercury is toxic to humans. For many years, spillage or leakage of mercury has been considered a hazard to dental patients, the dentist and staff workers. Leakage of mercury from the device may cause acute or chronic mercury toxicity through inhalation of mercury vapors. The agency believes that a performance standard is necessary to assure that dental amalgam capsules can safely be used to perform this mixing process without exposing patients and dental care workers to mercury vapors and because general controls alone are insufficient to control the risks to health presented by this device. A performance standard would provide reasonable assurance of the safety and effectiveness of the device. The agency also believes that there is sufficient information to establish a performance standard for this device.

Because the agency has determined that dental amalgam capsules should be classified into class II rather than class I, the agency is not required to publish a regulation adopting or rejecting the Panel recommendation that this device be exempt from the records and reports requirements under section 519 and the good manufacturing practice regulation under section 520(f) of the act.

On April 28, 1976, the agency terminated all of the device classification panels and reestablished them with the same functions, but with new names and a new structure. FDA published notices of these changes in the Federal Register of May 19, 1976 (43 FR 21660,, 21667, and 21668) and May 26, 1976 (43 FR 22672 and 22673). This proposed classification regulation identifies each device panel by the former name. Further information regarding the device advisory committees and list of their new names may be found in the preamble to the general provisions, published elsewhere in this issue of the Federal Register.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 513, 701(a), 52 Stat. 1055, 90 Stat. 540-540 (21 U.S.C. 360c, 371(a))) and under authority delegated to him (21 CFR 5.1), the Commissioner of Food and Drugs proposes to amend Part 872 in Subpart D by adding new § 872.3110, to read as follows:

§ 872.3110 Dental amalgam capsule.

(a) *Identification.* A dental amalgam capsule is a container device in which silver alloy is mixed with mercury to form dental amalgam.

(b) *Classification.* Class II (performance standards).

Interested persons may, on or before March 2, 1981, submit to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Four copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the Hearing Clerk docket number found in brackets in the heading

regulation classifying the device. These actions are being taken under the Medical Device Amendments of 19[illegible].

DATES: Comments by March 2, 1981. FDA proposes that the final regulation based on this proposal become effective 30 days after the date of its publication in the **Federal Register.**

ADDRESS: Written comments to the office of the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Gregory Singleton, Bureau of Medical Devices (HFK-460), Food and Drug Administration, 8757 Georgia Ave., Silver Spring, MD 20910, 301-427-7530.

SUPPLEMENTARY INFORMATION:

Panel Recommendation

A proposal elsewhere in this issue of the **Federal Register** provides background information concerning the development of the proposed regulation. The Dental Device Classification Panel, and FDA advisory committee, made the following recommendation regarding the classification of tooth shade resin materials:

1. Identification: Tooth shade resin material is a device composed of materials such as bisphenol-A and glycidyl methacrylate (Bis-GMA) that is used to restore carious lesions or structural defects in teeth.

2. Recommended classification: Class II (performance standards). The Panel recommends that establishing a performance standard for this device be a low priority.

3. Summary of reasons for recommendation: The Panel recommends that tooth shade resin materials be classified into class II because improper chemical composition of the resin may cause roughening of the restorative surface, which results in discoloration of tooth enamel and plaque accumulation on the tooth. The materials used in the device should meet a generally accepted satisfactory level of tissue compatibility. The Panel believes that general controls alone would not provide sufficient control over this characteristic. The Panel believes that a performance standard would provide reasonable assurance of safety and effectiveness of the device and that there is sufficient information to establish a performance standard.

4. Summary of data on which the recommendation is based: The Panel based its recommendation on the Panel members' personal knowledge of, and clinical experience with, the device in the practice of dentistry, and on an article by G. L. Lee, M.D., et al., (ref. 1). The article states that before a composite resin is used for restoration, the tooth enamel is etched with 50 percent phosphoric acid, which may irritate the tooth pulp.

5. Risks to health: (a) Periodontal disease: Discoloration and roughening of a restoration made with this device may cause plaque accumulation and lead to periodontal disease. (b) Pulp damage: Etching with 50 percent phosphoric acid before the restoration is completed may cause tooth pulp damage, unless the pulp is properly protected.

Proposed Classification

FDA agrees with the Panel recommendation and is proposing that tooth shade resin materials be classified into class II (performance standards). The agency believes that a performance standard is necessary for this device because general controls alone are insufficient to control the risks to health presented by the device. A performance standard would provide reasonable assurance of the safety and effectiveness of the device. The agency also believes that there is sufficient information to establish a performance standard for this device.

Reference

The following information has been placed in the office of the Hearing Clerk (address above) and may be seen by interested persons from 9 a.m. to 4 p.m., Monday through Friday.

1. Lee, G. L., J. A. Orlowski, C. C. Schidt, and R. L. Ihsen, "Histological Studies of an Adhesive Paint-on Restorative for Cervical Abrasions," *Australian Dental Journal*, 20:304-309, 1975.

On April 29, 1976, the agency terminated all of the device classification panels and reestablished them with the same functions, but with new names and a new structure. FDA published notices of these changes in the **Federal Register** of May 19, 1976 (43 FR 21666, 21667, and 21668) and May 20, 1976 (43 FR 22672 and 22673). This proposed classification regulation identifies each device panel by the former name. Further information regarding the device advisory committees and list of their new names may be found in the preamble to the general provisions, published elsewhere in this issue of the **Federal Register.**

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 513, 701(a), 52 Stat. 1055, 90 Stat. 540-549 (21 U.S.C. 360c, 371(a))) and under authority delegated to him (21 CFR 5.1), the Commissioner of Food and Drugs proposes to amend Part 872 in Subpart D by adding new § 872.3690, to read as follows:

§ 872.3690 Tooth shade resin material.

(a) *Identification.* Tooth shade resin material is a device composed of materials such as bisphenol-A glycidyl methacrylate (Bis-GMA) that is used to restore carious lesions or structural defects in teeth.

(b) *Classification.* Class II (performance standards).

Interested persons May, on or before March 2, 1981 submit to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Four copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the Hearing Clerk docket number found in brackets in the heading of this document. Received comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

Dated: November 19, 1980.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

[FR Doc. 80-38678 Filed 12-29-80; 8:45 am]

BILLING CODE 4110-03-M

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21 CFR Part 872

[Docket No. 78N-2294]

Medical Devices; Classification of Dental Mercury

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing for public comment a proposed regulation classifying dental mercury into class II (performance standards). FDA is also publishing the recommendation of the Dental Device Classification Panel that the device be classified into class II. The effect of classifying a device into class II is to provide for the future development of one or more performance standards to assure the safety and effectiveness of the device. After considering public comments, FDA will issue a final regulation classifying the device. These actions are being taken under the Medical Device Amendments of 1976.

DATES: Comments by March 2, 1981. FDA proposes that the final regulation based on this proposal become effective 30 days after the date of its publication in the **Federal Register.**

ADDRESS: Written comments to the office of the Hearing Clerk (HFA-305),

is to provide for the future development of one or more performance standards to assure the safety and effectiveness of the device. After considering public comments, FDA will issue a final regulation classifying the device. These actions are being taken under the Medical Device Amendments of 19[illegible].

DATES: Comments by March 2, 1981

members' personal knowledge of, and clinical experience with, the device in the practice of dentistry.

5. Risks to health: (a) Adverse tissue reaction: If the materials in the device are not biocompatible, the patient may have an adverse tissue reaction. (b) Toxic reaction: Alloys containing nickel and beryllium may cause a toxic reaction in the patient.

copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the Hearing Clerk docket number found in brackets in the heading of this document. Received comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

Dated: November 19, 1980.

Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Gregory Singleton, Bureau of Medical Devices (HFK-460), Food and Drug Administration, 8757 Georgia Ave., Silver Spring, MD 20910, 301-427-7530.

SUPPLEMENTARY INFORMATION:

Panel Recommendation

A proposal elsewhere in this issue of the **Federal Register** provides background information concerning the development of the proposed regulation. The Dental Device Classification Panel, an FDA advisory committee, made the following recommendation regarding the classification of dental mercury:

1. Identification: Dental mercury is a device composed of mercury that is used as a component of amalgam alloy in the restoration of dental cavities or broken teeth.

2. Recommended classification: Class II (performance standards). The Panel recommends that establishing a performance standard for this device be a high priority.

3. Summary of reasons for recommendation: The Panel recommends that dental mercury be classified into class II because the material in the device should meet a generally accepted satisfactory level of tissue compatibility. Dental mercury is a toxic substance and must be handled properly to control the hazards it presents. The Panel believes that general controls alone would not provide sufficient control over this characteristic.

The Panel believes that a performance standard would provide reasonable assurance of the safety and effectiveness of the device and that there is sufficient information to establish a performance standard.

4. Summary of data on which the recommendation is based: The Panel based its recommendation on the Panel members' personal knowledge of, and clinical experience with, the device in the practice of dentistry, and on an article published in the *Journal of the American Dental Association* "An Environmental Study of Mercury Contamination in Dental Offices" (Ref. *1*). The article discusses the hazards associated with use of mercury in dentistry and concludes that there is no danger of systemic poisoning for patients whose teeth have been restored with amalgam containing mercury. However, if proper procedures are not followed, there are potential hazards to those who handle mercury.

5. Risks to health: (a) Mercury poisoning: If the device is not handled properly, the user may suffer mercury poisoning from inhalation of mercury vapors. (b) Adverse tissue reaction: If the material in the device is not biocompatible, the patient may have an adverse tissue reaction.

Proposed Classification

FDA agrees with the Panel recommendation and is proposing that dental mercury be classified into class II (performance standards).

FDA has reviewed the medical literature on use of dental mercury in dentistry and has found evidence to support the Panel recommendation. Kawahara et al. concluded that the cytotoxicity of the amalgam is related to free mercury available after mixing the alloy and the mercury, but that cytotoxicity was nearly nonexistent after complete setting of the amalgam (Ref. *2*). Cataldo and Santis studied the results of implantation of amalgam into the oral tissues (Ref. *3*). Encapsulation in connective tissue occurred with the smallest pieces of amalgam without inflammatory response, and larger pieces had connective tissue encapsulation with some macrophage (microorganism) response. The agency believes that a performance standard is necessary for this device because general controls alone are insufficient to control the risks to health presented by this device. A performance standard would provide reasonable assurance of the safety and effectiveness of the device. The agency also believes that there is sufficient information to establish a standard for this device.

References

The following information has been placed in the office of the Hearing Clerk (address above) and may be seen by interested persons from 9 a.m. to 4 p.m., Monday through Friday.

1. "An Environmental Study of Mercury Contamination in Dental Offices," *Journal of the American Dental Association*, Vol. 89, Nov. 1974.

2. Kawahara, H., et al., "Cellular Responses to Dental Amalgam In-Vitro," *Journal of Dentistry Research*, 54(2):394-401, March-April 1975.

3. Cataldo, E., and H. Santis, "Response of the Oral Tissue to Exogenous Foreign Materials," *Journal of Periodontics*, 45(2):93-100, February 1974.

On April 28, 1976, the agency terminated all of the device classification panels and reestablished them with the same functions, but with new names and a new structure. FDA published notices of these changes in the **Federal Register** of May 19, 1976 (43 FR 21630, 21667, and 21668) and May 20, 1976 (43 FR 22072 and 22073). This proposed classification regulation identifies each device panel by the former name. Further information regarding the device advisory committees and list of their new names may be found in the preamble to the general provisions, published elsewhere in this issue of the **Federal Register.**

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 513, 701(e), 52 Stat. 1055, 90 Stat. 540-540 (21 U.S.C. 360c, 371(e))) and under authority delegated to him (21 CFR 5.1), the Commissioner of Food and Drugs proposes to amend Part 872 in Subpart D by adding new § 872.3700, to read as follows:

§ 872.3700 Dental mercury.

(a) *Identification.* Dental mercury is a device composed of mercury that is used as a component of amalgam alloy in the restoration of dental cavities or broken teeth.

(b) *Classification.* Class II (performance standards).

Interested persons may, on or before March 2 submit to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Four copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the Hearing Clerk docket number found in brackets in the heading of this document. Received comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

Dated: November 19, 1980.

William F. Randolph,
Acting Associate Commissioner for Regulatory Affairs.

[FR Doc. 80-39077 Filed 12-29-80; 8:45 am]
BILLING CODE 4110-03-M

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21 CFR Part 872

[Docket No. 78N-2895]

Medical Devices; Classification of Base Metal Alloys

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing for public comment a proposed regulation classifying base metal alloys into class II (performance standards). FDA is also publishing the recommendation of the Dental Device Classification Panel that the device be classified into class II. The effect of classifying a device into class II

1. Identification: A pantograph is a device that is attached to a patient's head and is used to duplicate lower jaw movements to aid in the construction of restorative and prosthetic dental devices. A marking pen is attached to [illegible] component of the device.

the act, the agency may exempt a manufacturer from section 510 only if it finds that compliance with this section is not necessary for the protection of the public health. In the case of registration and listing by manufacturers of pantographs, the agency cannot make [illegible] To protect the

good manufacturing practice (GMP) regulation under section 520(f) of the act (21 U.S.C. 360j(f)), FDA is proposing that a manufacturer of this device be exempt, in the manufacture of the device, from all requirements in the GMP regulation except § 820.180 (21 CFR 820.180), with respect to general requirements [illegible] and 121

Ex. 7

Federal Register

Wednesday
August 12, 1987

Part VI

Department of Health and Human Services

Food and Drug Administration

21 CFR Part 872

Medical Devices; Dental Devices Classification; Final Rule and Withdrawal of Proposed Rules

DEPARTMENT OF HEALTH AND HUMAN SERVICES

21 CFR Part 872

[Docket No. 78N-2630]

Dental Devices; General Provisions and Classifications of 110 Devices

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is classifying 110 dental devices. The preamble to this rule responds to comments received on the proposed regulations regarding classification of these devices. These actions are being taken under the Medical Device Amendments of 1976.

EFFECTIVE DATE: September 11, 1987.

FOR FURTHER INFORMATION CONTACT: Gregory Singleton, Center for Devices and Radiological Health (HFZ-470), Food and Drug Administration, 8757 Georgia Ave., Silver Spring, MD 20910, 301-427-7555.

SUPPLEMENTARY INFORMATION:

Table of Contents

A. Background

In the **Federal Register** of December 30, 1980 (45 FR 85902-86108), FDA published proposed regulations containing general provisions applicable to the classification of dental devices and individual proposed regulations to classify dental devices in commercial distribution into one or more of three regulatory classes: Class I (general controls), class II (performance standards), and class III (premarket approval).

In this final rule, FDA is classifying 110 devices as follows: 53 devices into class I, 42 devices into class II, 10 devices into class III, and, depending upon a variety of factors, such as intended uses or composition of the devices, 2 devices into class I or class II, 2 devices into class I or class III, and 1 device into class II or class III. To reduce printing costs, FDA is publishing the general provisions and the classifications in one final rule. FDA previously published a separate proposed classification rule and final classification rule for each device.

Classification of medical devices in commercial distribution is required by the Medical Device Amendments of 1976 (Pub. L. 94-295) (the amendments) to the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 301-392). The effect of classifying a device into class I is to require that the device continue to meet only the general controls applicable to all devices. The effect of classifying a device into class II is to provide for the future development of one or more performance standards to assure the safety and effectiveness of the device. The effect of classifying a device into class III is to require each manufacturer of the device to submit to FDA a premarket approval application that includes information concerning safety and effectiveness tests for the device. For a class III device not considered a new drug before the amendments that either was in commercial distribution before May 28, 1976, or that is substantially equivalent to a device that was in commercial distribution before that date, each application for premarket approval must be submitted to FDA on or before February 28, 1990, or 90 days after promulgation of a separate regulation requiring premarket approval of the device, whichever occurs later. Devices that FDA previously regarded as new drugs, or newly offered devices that are not substantially equivalent to a device that was in commercial distribution before the amendments, are classified by statute into class III and already are required to have in effect an approved application for premarket approval. See sections 520(l) and 513(f) of the act (21 U.S.C. 360j(l), 360c(f)).

The preamble to the proposed regulations described the development of the general provisions and the proposed regulations classifying dental devices and the activities of the Dental Device Section of the Ophthalmic, Ear, Nose, and Throat; and Dental Devices Panel, now the Dental Device Panel (the Panel), an FDA advisory committee that makes recommendations to FDA concerning the classification of dental devices. FDA provided a period of 60 days, later extended to 90 days (March 6, 1981; 46 FR 15519), for interested persons to submit written comments on the proposals. The comments received and FDA's responses to the comments are discussed below.

In April 1985, H.R. 2177 (99th Cong. 1st Sess.) was introduced in the U.S. House of Representatives. The bill was a legislative proposal of the Department of Health and Human Services. Among other things, the bill would have (1) amended the act to eliminate the statutory category of class II, (2) made the establishment of a performance standard one of the several general controls that may be made applicable to a device, and (3) streamlined the procedure for establishing standards required by section 514 of the act. If legislation comparable to this bill becomes law, there would be only two categories of devices: class I (general controls) and class II (premarket approval, currently class III). Class II devices would be redesignated as class I devices. Because the proposed legislation contains transitional provisions that convert classifications under the current law to classifications under the proposed law, FDA is continuing to issue classification rules under the current law.

B. FDA's Priorities for Establishing Performance Standards

In the **Federal Register** of October 23, 1985 (50 FR 43000), FDA published a notice, "Policy Statement; Class III Medical Devices," announcing its policy for setting priorities for initiating proceedings to establish performance standards for medical devices classified into class II. Under the amendments, FDA is required to establish performance standards for class II devices. At this time, however, FDA does not have the resources to establish performance standards for all the devices already classified for being classified) in class II. Under the amendments, FDA is using the regulatory controls of class I to regulate a device classified into class II until a performance standard is established under section 514 of the act (21 U.S.C. 360d) for a class II device. In the notice above FDA announced it will consider the following factors when setting priorities for establishing performance standards for class II devices:

a. The seriousness of questions concerning the safety and effectiveness of the device; the risks associated with use of the device; the significance of a device to the public health; and the present and projected use of the device;

b. The recommendations of FDA's advisory committees;

c. The impact of an FDA guideline or recommendation;

d. The effect of a Federal standard or other regulatory controls under an authority other than the act;

e. The impact of voluntary standards;

f. The impact of activities authorized under the general controls provisions of the act;

g. The effect of dissemination of information and education efforts;

h. The sufficiency of voluntary corrective actions;

i. Valid scientific evidence developed since classification;

j. The existence of a petition for reclassification;

k. The impact of any other factors that affect a device's safety or effectiveness.

C. Changes in the Name of the Dental Device Advisory Committee

FDA has periodically reorganized its advisory panels for device classification. Most recently, on April 14, 1984, FDA established the Dental Devices Panel (see 49 FR 17446; April 24, 1984). The new panel performs the same functions with respect to dental devices as did its predecessors, the Dental Device Classification Panel (1976–1978) and the Ophthalmic; Ear, Nose, and Throat; and Dental Devices Panel (1978–1984). Because of several changes in the membership of the advisory committee for dental devices that occurred after the committee had made its classification recommendations, during July 1981, FDA requested the committee to review its original classification recommendations. The new committee reaffirmed all but two of the old committee's recommendations (see paragraphs 11 and 13 of this preamble for the changes).

D. Grouping of Similar Devices—Withdrawal of 67 Dental Proposed Regulations Because of Different Grouping

In this final rule, FDA has grouped together similar devices, thereby reducing the number of separate dental device classifications. FDA issued proposals on 185 devices and is issuing final classifications now on 110 devices, with 10 additional classifications planned in the future.

FDA has now grouped 99 dental devices that were the subjects of FDA's proposals as separate generic types of devices into 22 generic types of devices, thus eliminating the need for 67 final classifications. Elsewhere in this issue of the **Federal Register**, FDA is withdrawing the 67 proposed dental device classification regulations that now are unnecessary due to the new grouping of dental devices. The remaining 96 generic types of devices that were the subjects of proposals are unaffected by this regrouping. The term "generic type of device" is defined in 21 CFR 860.3(l). Dental devices that are grouped into one generic type of device do not differ significantly in purpose, design, materials, energy source, function, or any other feature related to safety or effectiveness. Consequently, similar regulatory controls are appropriate to provide reasonable assurance of the safety and effectiveness of these devices. FDA has made appropriate changes in the identification of each device being grouped in order to identify more accurately the generic type of device.

The devices being grouped differently from the proposals are identified in this preamble below under "F. LIST OF DENTAL DEVICES." Each generic type of dental device is identified with both the docket number or numbers used for that device in the proposed regulations and the section number of the Code of Federal Regulations at which its classification is being codified. A device listed in the "List of Dental Devices" that is not identified with a section number is being grouped into the generic type of device with a section number listed directly before it. (Thus, for example, *Gold based alloy for clinical use* and *Precious metal alloy for clinical use* are being grouped into the generic type of device *Gold based alloys and precious metal alloys for clinical use* (§ 872.3060)).

The new grouping of dental devices results in 110 generic types of dental devices (185 proposals minus 67 unnecessary proposals). FDA is postponing for now its final classifications of 10 generic types of electrically powered dental devices pending the agency's review of additional data concerning electrical safety (see the next section of this preamble, "E. DENTAL DEVICES NOT BEING CLASSIFIED AT THIS TIME"). Thus, the number of generic types of dental devices based on the 1980 proposals that are being classified in this rule is 100.

Also, in this final rule, FDA is codifying the classifications of two devices that, under applicable statutory procedures, need not have been subjects of proposed classification rules (see the discussions under "K. CODIFICATION OF TWO DEVICES NOT SUBJECTS OF DENTAL PROPOSED REGULATIONS"). With these two additional classifications, in this rule FDA is classifying 110 generic types of dental devices.

E. Dental Devices not Being Classified at This Time

FDA is postponing classification of the following 10 generic types of dental devices in order to review additional data on electrical safety. FDA is considering reproposing these devices for classification into class I. Because of the grouping of similar dental devices as described above, the 10 generic types of devices encompass devices that were the subjects of 20 proposed regulations. The following is a list of the 10 generic types of dental devices that are not being classified in this final rule:

Mechanical denture cleaner
Dental handpiece and accessories
Dental chair with or without operative unit
Oral irrigation unit
Dental operative unit and accessories
Powered toothbrush
AC-powered dental amalgamator
Fiber optic dental light
Heat source for bleaching teeth
Boiling water sterilizer

F. List of Dental Devices

The list below shows, for each dental device, the section of the Code of Federal Regulations at which the classification of that device is being codified (or will be codified), the docket number or numbers of any corresponding proposed classification regulation, and the final classification of the device.

The list includes the 10 generic types of dental devices for which final classification is being postponed. For each of these 10 devices, the section number of the Code of Federal Regulations is in parentheses, the name of the device is identified with footnote "*", and no final classification is provided.

Section	Device	Docket No.	Class
	Subpart B—Diagnostic Devices		
872.1500	Gingival fluid measurer	78N-2831	I
872.1720	Pulp tester	78N-2834	II
872.1730	Electrode gel for pulp tester	78N-2835	I

Section	Device	Docket No.	Class
872.1740	Caries detection device	80P-0064	II
872.1800	Extraoral source X-ray system	78N-2836	II
872.1810	Intraoral source X-ray system	78N-2837	II
872.1820	Dental X-ray exposure alignment device	78N-2838	I
872.1830	Cephalometer	78N-2839	II
872.1840	Dental X-ray position indicating device	78N-2840	II
872.1850	Lead-lined position indicator	78N-2841	II
872.1905	Dental X-ray film holder	78N-2842	I
	SUBPART D—PROSTHETIC DEVICES		
872.3050	Amalgam alloy	78N-2843	II
872.3060	Gold based alloys and precious metal alloys for clinical use	78N-2844	II
	Gold based alloy for clinical use	78N-2844	
	Precious metal alloy for clinical use	78N-2845	
872.3080	Mercury and alloy dispenser	78N-2846	I
(872.3100)	AC-powered dental amalgamator [4]	78N-2847	
872.3110	Dental amalgam capsule	78N-2848	I
872.3130	Preformed anchor	78N-2849	I
872.3140	Resin applicator	78N-3024	I
872.3150	Articulator	78N-2850	I
872.3165	Precision attachment	78N-2851	I
	Precision attachment	78N-2851	
	Preformed bar	78N-2852	
872.3200	Resin tooth bonding agent	78N-2853	II
872.3220	Facebow	78N-2854	I
872.3240	Dental bur	78N-2855	I
872.3250	Calcium hydroxide cavity liner	78N-2856	II
872.3260	Cavity varnish	78N-2857	II
872.3275	Dental cement	78N-2858	I, II
	Dental cement	78N-2858	
	Zinc oxide eugenol	78N-2913	
872.3285	Preformed clasp	78N-2859	I
	Preformed clasp	78N-2859	
	Preformed wire clasp	78N-2860	
872.3300	Hydrophilic resin coating for dentures	78N-2861	II
872.3310	Coating material for resin fillings	78N-2862	II
872.3330	Preformed crown	78N-2863	I
872.3350	Gold or stainless steel cusp	78N-2864	I
872.3360	Preformed cusp	78N-2865	I
872.3400	Karaya and sodium borate with or without acacia denture adhesive	78N-2866	I, III
	Acacia and karaya with sodium borate denture adhesive	78N-2866	
	Karaya with sodium borate denture adhesive	78N-2873	
872.3410	Ethylene oxide homopolymer and/or carboxymethylcellulose sodium denture adhesive	78N-2867	I
	Carboxymethylcellulose sodium (40 to 100%) denture adhesive	78N-2867	
	Carboxymethylcellulose sodium (32%) and ethylene oxide homopolymer (13%) denture adhesive	78N-2869	
	Carboxymethylcellulose sodium (49%) and ethylene oxide homopolymer (21%) denture adhesive	78N-2870	
872.3420	Carboxymethylcellulose sodium and cationic polyacrylamide polymer denture adhesive	78N-2868	III
872.3450	Ethylene oxide homopolymer and/or karaya denture adhesive	78N-2871	I
	Karaya denture adhesive	78N-2871	
	Karaya and ethylene oxide homopolymer denture adhesive	78N-2872	
872.3480	Polyacrylamide polymer (modified cationic) denture adhesive	78N-2874	III
872.3490	Carboxymethylcellulose sodium and/or polyvinylmethylether maleic acid calcium-sodium double salt denture adhesive.	78N-2875	I
	Polyvinylmethylether maleic acid calcium-sodium double salt denture adhesive	78N-2875	
	Polyvinylmethylether maleic acid calcium-sodium double salt and carboxymethylcellulose sodium denture adhesive.	78N-2877	
872.3500	Polyvinylmethylether maleic anhydride (PVM-MA), acid copolymer, and carboxymethylcellulose sodium (NACMC) denture adhesive.	78N-2876	III
872.3520	OTC denture cleanser	78N-2878	I
(872.3530)	Mechanical denture cleaner [4]	78N-2879	
872.3540	OTC denture cushion or pad	78N-2880	I, III
	OTC denture cushion	78N-2880	
	OTC denture pad	78N-2881	
872.3560	OTC denture reliner	78N-2882	III
872.3570	OTC denture repair kit	78N-2883	III
872.3580	Preformed gold denture tooth	78N-2884	I
872.3590	Preformed plastic denture tooth	78N-2885	II
872.3600	Partially fabricated denture kit	78N-2886	III
872.3640	Endosseous implant	78N-2887	III
872.3645	Subperiosteal implant material	78N-2888	II
	Titanium subperiosteal implant material	78N-2888	
	Cobalt chrome molybdenum subperiosteal implant material	78N-2889	
872.3660	Impression material	78N-2890	II

Section	Device	Docket No.	Class
872.3670	Resin impression tray material	78N-2891	I
872.3680	Polytetrafluoroethylene (PTFE) ytreous carbon material	78N-2892	II
872.3690	Tooth shade resin material	78N-2893	II
872.3700	Dental mercury	78N-2894	I
872.3710	Base metal alloy	78N-2895	II
872.3730	Pantograph	78N-2897	I
872.3740	Retentive and splinting pin	78N-2898	I
872.3750	Bracket adhesive resin and tooth conditioner	78N-2899	II
872.3760	Denture relining, repairing, or rebasing resin	78N-2900	II
872.3765	Pit and fissure sealant and conditioner	78N-2901	II
872.3770	Temporary crown and bridge resin	78N-2902	II
872.3810	Root canal post	78N-2904	I
872.3820	Root canal filling resin	78N-2905	II, III
872.3830	Endodontic paper point	78N-2906	I
872.3840	Endodontic silver point	78N-2907	I
872.3850	Gutta percha	78N-2908	I
872.3890	Endodontic stabilizing splint	78N-2909	II
872.3900	Posterior artificial tooth with a metal insert	78N-2910	I
872.3910	Backing and facing for an artificial tooth	78N-2911	I
872.3920	Porcelain tooth	78N-2912	II
872.3930	Tricalcium phosphate granules for dental bone repair		III
	SUBPART E—SURGICAL DEVICES		
872.4120	Bone cutting instruments and accessories	78N-2915	II
	Manual bone drill and wire driver	78N-2916	I
	Powered bone drill	78N-2917	I
	Rotary bone cutting handpiece	78N-2920	I
	AC-powered bone saw	78N-2941	I
872.4130	Intraoral dental drill	78N-2918	II
(872.4200)	Dental handpiece and accessories [1]	78N-2918	I
	Air-powered dental handpiece	78N-2918	I
	Belt-driven dental handpiece	78N-2919	I
	Contra angle handpiece attachment	78N-2921	I
	Direct drive handpiece	78N-2922	I
	Foot controller for handpiece	78N-2923	I
	Water-powered handpiece	78N-2924	I
872.4465	Gas-powered jet injector	78N-2925	II
872.4475	Spring-powered jet injector	78N-2926	II
872.4535	Dental diamond instrument	78N-2929	I
872.4565	Dental hand instrument	78N-2931	I
	Dental hand instrument	78N-2931	I
	Endodontic broach	78N-3027	I
	Dental wax carver	78N-2914	I
	Endodontic pulp canal file	78N-3026	I
	Hand instruments for calculus removal	78N-2927	I
	Dental depth gauge instrument	78N-2928	I
	Plastic dental filling instrument	78N-2930	I
	Dental instrument handle	78N-2932	I
	Surgical tissue scissors	78N-2945	I
	Orthodontic band driver	78N-2952	I
	Orthodontic band pusher	78N-2954	I
	Orthodontic band setter	78N-2955	I
	Orthodontic bracket aligner	78N-2958	I
	Orthodontic pliers	78N-2962	I
	Orthodontic ligature tucking instrument	78N-2967	I
	Forceps for articulation paper	78N-2990	I
	Forceps for dental dressing	78N-2991	I
	Dental matrix band	78N-2997	I
	Matrix retainer	78N-2998	I
	Mouth mirror	78N-3000	I
	Dental retractor	78N-3007	I
	Dental retractor accessories	78N-3008	I
	Periodontic or endodontic irrigating syringe	78N-3016	I
	Restorative or impression material syringe	78N-3017	I
872.4600	Intraoral ligature and wire lock	78N-2933	II
(872.4620)	Fiber optic dental light [1]	78N-2934	I
872.4630	Dental operating light	78N-2935	II
	Dental operating light	78N-2935	I
	Surgical headlight	78N-2936	I
872.4730	Dental injecting needle	78N-2937	I
872.4760	Bone plate	78N-2938	II
872.4840	Rotary scaler	78N-2942	II
872.4850	Ultrasonic scaler	78N-2943	II

Section	Device	Docket No.	Class
872.4880	Intraosseous fixation screw or wire	78N-2946	II
	Intraosseous fixation screw	78N-2946	
	Intraosseous fixation wire	78N-2946	
872.4920	Dental electrosurgical	78N-2947	II
	SUBPART F—THERAPETIC DEVICES		
872.5410	Orthodontic appliance and accessories	78N-2951	I
	Preformed orthodontic band	78N-2951	
	Orthodontic elastic band	78N-2950	
	Orthodontic band material	78N-2953	
	Orthodontic metal bracket	78N-2956	
	Orthodontic wire clamp	78N-2959	
	Preformed orthodontic space maintainer	78N-2961	
	Orthodontic expansion screw retainer	78N-2963	
	Orthodontic spring	78N-2964	
	Orthodontic tube	78N-2968	
	Orthodontic wire	78N-2968	
872.5470	Orthodontic plastic bracket	78N-2957	II
872.5500	Extraoral orthodontic headgear	78N-2960	II
872.5525	Preformed tooth positioner (proposed as § 872.5575)	78N-3025	I
872.5550	Teething ring	78N-2965	I, II
	SUBPART G—MISCELLANEOUS DEVICES		
872.6010	Abrasive device and accessories	78N-2969	I
	Abrasive disk	78N-2969	
	Guard for an abrasive disk	78N-2993	
	Abrasive point	78N-2970	
	Polishing agent strip	78N-2972	
	Polishing wheel	78N-2973	
872.6030	Oral cavity abrasive polishing agent	78N-2971	I
872.6060	Saliva absorber	78N-2974	I
	Paper saliva absorber	78N-2974	
	Cotton roll	78N-2982	
872.6070	Ultraviolet activator for polymerization	78N-2975	II
872.6080	Airbrush	78N-2976	III
872.6100	Anesthetic warmer	78N-2977	I
872.6140	Articulation paper	78N-2978	I
872.6200	Base plate shellac	78N-2979	I
(872.6250)	Dental chair with or without operative unit [3]	78N-2980	
	Dental chair with operative unit	78N-2980	
	Dental chair without operative unit	78N-2981	
872.6290	Prophylaxis cup	78N-2983	I
872.6300	Rubber dam and accessories	78N-2984	I
	Rubber dam	78N-2984	
	Rubber dam clamp	78N-2985	
	Rubber dam frame	78N-2986	
	Forceps for a rubber dam clamp	78N-2992	
872.6350	Ultraviolet detector	78N-2987	II
872.6390	Dental floss	78N-2989	I
(872.6475)	Heat source for bleaching teeth [3]	78N-2994	
(872.6510)	Oral irrigation unit [3]	78N-2996	
872.6570	Impression tube	78N-2999	I
(872.6640)	Dental operative unit and accessories [3]	78N-3002	
	Dental operative unit	78N-3002,	
	Saliva ejector mouthpiece	78N-3001	
	Oral cavity evacuator	78N-2988	
	Suction operative unit	78N-3003	
	Air or water syringe unit	78N-3012	
872.6650	Massaging pick or tip for oral hygiene	78N-3004	I
	Massaging pick	78N-3004	
	Rubber tip for oral hygiene	78N-3018	
872.6660	Porcelain powder for clinical use	78N-3005	II
872.6670	Silicate Protector	78N-3006	I
(872.6710)	Boiling water sterilizer [3]	78N-3009	
872.6730	Endodontic dry heat sterilizer	78N-3011	III
872.6770	Cartridge syringe	78N-3014	II
872.6855	Manual toothbrush	78N-3010	I
(872.6865)	Powered toothbrush [3]	78N-3020	
872.6870	Disposable fluoride tray	78N-3021	I
872.6880	Preformed impression tray	78N-3022	I
872.6890	Intraoral dental wax	78N-3023	I

[1] Not proposed; classification results from FDA's decision on a reclassification petition.
[2] Classification postponed.
[3] Not proposed; statutory classification.

G. Changes in Classifications

Based on the comments received and on additional consideration of all information before the agency, FDA has placed several devices in different classes from those originally proposed. FDA's reasons for adopting classifications for these devices that differ from the proposals are provided in this preamble in the section that follows. FDA believes that it is not necessary to issue a new proposal concerning these decisions. The purpose of publishing a proposal and soliciting comments is to enable the agency to determine whether its proposed classification of a device was correct. After reviewing the comments submitted on a proposal, the agency may be persuaded that its proposed classification is incorrect. Persons interested in the classification process should therefore anticipate that in a final regulation a device may be placed in a class different from the one originally proposed. This possibility was specifically identified in the proposed general regulation on dental devices (see 45 FR 85904). In addition, many of the final classifications that differ from FDA's proposed classifications are consistent with the recommendations of the Panel. These recommendations were published in the preambles to the proposed rules and thus foreshadowed the changes now being made. Persons who disagree with the final classification of a device may petition for reclassification of the device under Subpart C of Part 860 (21 CFR Part 860).

H. Summary of Comments on Classifications and FDA's Responses

To clarify the final rule and save printing costs, FDA is responding once to comments that apply to more than one dental device. In such cases, FDA's response identifies the devices to which the comment and response apply.

1. Many comments on the proposed regulations requested that FDA classify each dental device into the class recommended by the Panel.

FDA's final classification rule accomplishes many, but not all, of the changes desired by these general comments. Of the 165 devices that were the subjects of the proposed regulations, FDA proposed to classify 108 devices (58 percent) into the class recommended by the Panel. Taking into account the Panel's later changes in its recommendations on two devices (see paragraphs 11 and 13 of this preamble) and omitting the 10 final classifications which are being postponed, in this final rule FDA is classifying about 89 percent of the devices into the class recommended by the Panel. FDA is making available (Ref. 12) in its Docket Management Branch (address below) a detailed matrix that shows for each device how the Panel's recommendations compare to FDA's proposed and final classifications.

2. Many comments requested that FDA classify into class I most of the 124 dental devices that FDA proposed to classify into class II.

FDA agrees in part and disagrees in part with the comments. For many of the 77 devices that the Panel recommended be placed in class I but which FDA proposed to classify into class II, FDA now agrees that the correct class is class I. Accordingly, in the final rule the agency is classifying many of these devices into class I. However, the Panel recommended and FDA proposed that 47 dental devices be classified into class II. For many of these 47 devices, FDA disagrees with the comments requesting that these devices be placed into class I. In the paragraphs below, FDA is providing its reasons for agreeing or disagreeing with these comments with respect to specific devices.

3. In addition to the comments discussed above in paragraphs 1 and 2, specific comments on the proposed regulations on the devices discussed below argued that the agency did not identify any substantive risks to health associated with the devices that would justify classifying them into class II, as was proposed by FDA. The section had recommended that these devices be classified into class I, with the exception of the dental diamond instrument (§ 872.4535) and hand instrument for calculus removal (Docket No. 78N-2027), which the section had recommended be classified into class II.

Comments stated that the agency cited no adverse experience data or complaint data to support the proposed classifications. The comments reasoned that the devices should be classified into class I because manufacturers have distributed these devices for many years without FDA controls and because they are safe and effective. FDA has considered these comments in the classification decisions described below.

3a. Dental x-ray exposure alignment device (§ 872.1020).

FDA now believes that the dental x-ray exposure alignment device, an accessory to a dental x-ray system, should be classified into class I. FDA proposed to classify the device into class II because of concern about improper x-ray beam alignment that, in some instances, may cause the operator of the dental x-ray system to repeat x-rays of patients. If x-rays have to be repeated, the patient would receive unnecessary radiation. However, FDA now believes that the accuracy of dental x-ray beam alignment depends almost entirely on the skills of the operator of the dental x-ray system, and only a limited portion of the risk of improper x-ray beam alignment results from the design and function of the dental x-ray exposure alignment device. FDA believes that it is unnecessary to establish performance standards for the dental x-ray exposure alignment device, because the essential portion of the risk to health of improper alignment of the x-ray beam would not be significantly reduced through establishment of a standard for the accessory device. FDA believes that the general controls of class I alone would provide reasonable assurance of the safety and effectiveness of the device. Accordingly, FDA is classifying the dental x-ray exposure alignment device into class I.

3b. Dental retractor (Docket No. 78N-3007); dental retractor accessories (Docket No. 78N-3006); and dental x-ray film holder (§ 872.1905).

FDA now believes that the three devices above should be classified into class I. FDA proposed to classify these devices into class II because of concerns about microbial contamination of the reusable devices that may cause infections in patients. FDA now believes that the essential risk to health from microbial contamination of these reusable devices is controlled by the skill and conscientiousness of the users of these devices in maintaining the cleanliness of the devices and sterilizing them between uses. FDA believes that it is unnecessary to establish performance standards for the devices above, because the essential risk to health (microbial contamination) would not be reduced through establishment of standards. FDA believes that the general controls of class I alone would provide reasonable assurance of the safety and effectiveness of these devices, particularly the controls of the current good manufacturing practice (CGMP) regulations in Part 820. Accordingly, FDA is classifying the dental retractor, dental retractor accessories, and the dental x-ray film holder into class I.

3c. Mercury and alloy dispenser (§ 872.3090) and dental amalgam capsule (§ 872.3110).

FDA now believes that the mercury and alloy dispenser and the dental amalgam capsule should be classified into class I. FDA proposed to classify the devices above into class II because of concern about the accuracy of measurements of materials by the

mercury and alloy dispenser, and concern that both devices might leak mercury that may cause toxic reactions. FDA now believes that the risk to health of patients presented by inaccurate measurements of materials by the mercury and alloy dispenser is minimal and this risk would be controlled by manufacturers' adherence to the CGMP regulations. FDA also believes that manufacturers' adherence to the CGMP regulations for these devices would control the potential for leakage of mercury from the devices that could pose a risk to health of dental practitioners. (See also paragraph 5 for a discussion of classification of dental mercury.) Thus, FDA now believes that it is unnecessary to establish performance standards for the two devices, because the devices present a low risk to health of patients, and these risks would not be significantly reduced through establishment of such standards. FDA believes that the general controls of class I alone would provide reasonable assurance of the safety and effectiveness of the two devices, particularly the controls of the CGMP regulations in Part 820. Accordingly, FDA is classifying the mercury and alloy dispenser and the amalgam capsule into class I.

3d. Intraoral dental drill (§ 872.4130) and dental diamond instrument (§ 872.4535).

FDA now believes that the intraoral dental drill and the dental diamond instrument should be classified into class I. FDA proposed to classify the devices into class II because of concerns about the strength and hardness of the intraoral dental drill and the possibility of inadequate abrasive properties of the dental diamond instrument. Both devices are intended to cut human teeth. FDA now believes that minimal risk to the health of patients would result, if the intraoral dental drill were to lack strength and hardness or if the dental diamond instrument were to lack certain abrasive properties. FDA also believes that these risks to health would be controlled through the general controls of class I, particularly manufacturers' adherence to the CGMP regulations in Part 820. FDA now believes that is is unnecessary to establish performance standards for the devices. FDA believes that the general controls of class I alone would provide reasonable assurance of the safety and effectiveness of the devices. Accordingly, FDA is classifying the intraoral dental drill and the dental diamond instrument into class I.

3e. Hand instrument for calculus removal (Docket No. 78N-2927).

FDA now believes that the hand instrument for calculus removal should be classified into class I. FDA proposed to classify the device into class II because of concern that improper design of the device might cause unnecessary trauma to gum tissue and concern that lack of biocompatibility of the device might cause adverse tissue reactions. (FDA is discussing the latter concern in paragraph 3f., below.) FDA now believes that minimal risk to health would result, if this hand-held device were to have an improper design. The device is intended for use by dental health professionals experienced in its use. Trauma to a patient's gums from use of the device is essentially controlled by the skills of the professional using it, and the device itself would rarely, if ever, be responsible for unnecessary gum trauma. Thus, FDA believes that it is unnecessary to establish performance standards to control the design of the device, because the essential portion of the risk to health of unnecessary gum trauma would not be reduced through establishment of standards for the device. FDA believes that the general controls of class I alone would provide reasonable assurance of the safety and effectiveness of the hand instrument for calculus removal. Accordingly, FDA is classifying the device into class I.

3f. FDA now believes that the devices listed below should be classified into class I. FDA proposed to classify the devices into class II because of concerns about possible biocompatibility of the devices, resulting in adverse tissue reactions. However, FDA now believes that in 1980, when it proposed to classify these devices, the agency assigned to the devices a higher level of risk of biocompatibility than was justified by the years of experience of dentists and patients with these devices.

Thus, FDA now believes that it is unnecessary to establish performance standards for the devices listed below to control the risk of biocompatibility, because FDA believes that these devices present only minimal risks of biocompatibility and that these minimal risks would not be significantly reduced through establishing performance standards for these devices due to the idiosyncratic nature of individual sensitivities. FDA believes that the general controls of class I would provide reasonable assurance of the safety and effectiveness of the devices. The labeling of a device that causes sensitivity reactions in some individuals should be so labeled, to be in compliance with the misbranding provisions (21 U.S.C. 352) of the general controls of the act. Accordingly, FDA is classifying the devices listed below in class I.

Section	Device/Docket No.
872.1730	Electrode gel for pulp tester.
872.3410	Ethylene oxide homopolym and/or carboxymethylcellulo sodium denture adhesive.
	Carboxymethylcellulose sodi (40 to 100%) denture adhes (Docket No. 78N-2867).
	Carboxymethylcellulose sodi (32%) and ethylene oxide h mopolymer (13%) denture a hesive (Docket No. 78N-286
	Carboxymethylcellulose sodi (49%) and ethylene oxide h mopolymer (21%) denture a hesive (Docket No. 78N-287
872.3450	Ethylene oxide homopolym and/or karaya denture adh sive.
	Karayra denture adhesive (Dock No. 78N-2871).
	Karaya and ethylene oxide hom polymer denture adhesi (Docket No. 78N-2872).
872.3490	Carboxymethylcellulose sodi and/or polyvinylmethyleth maleic acid calcium-sodi double salt denture adhesiv
	Polyvinylmethylether maleic ac calcium-sodium double s denture adhesive (Docket N 78N-2875).
	Polyvinylmethylether maleic ac calcium-sodium double salt ca boxymethylcellulose sodiu denture adhesive (Docket N 78N-2877).
872.3520	OTC denture cleanser.
872.3630	Endodontic paper point.
872.3640	Endodontic silver point.
872.3650	Gutta percha.
872.4565	Dental hand instrument.
	Endodontic broach (Docket N 78N-3027).
	Endodontic pulp canal (Docket No. 78N-3026).
	Surgical tissue scissors (Docke No. 78N-2951).
872.5410	Orthodontic appliances access ries.
	Preformed orthodontic ban (Docket No. 78N-2951).
	Orthodontic elastic band (Docke No. 78N-2950).
	Orthodontic band materia (Docket No. 78N-2953).
	Orthodontic metal bracke (Docket No. 78N-2956).
	Orthodontic wire clamp (Docke No. 78N-2959).
	Preformed orthodontic spac maintainer (Docket No. 78N 2961).
	Orthodontic expansion screw re tainer (Docket No. 78N-2963)
	Orthodontic spring (Docket No 78N-2964).
	Orthodontic tube (Docket No 78N-2966).
	Orthodontic wire (Docket No 78N-2968).
872.5525	Preformed tooth positioner.

Section	Device/Docket No.
872.6010	Abrasive device and accessories.
	Abrasive disk (Docket No. 78N-2969).
	Abrasive point (Docket No. 78N-2970).
	Polishing agent strip (Docket No. 78N-2972).
872.6030	Oral cavity abrasive polishing agent.
872.6200	Base plate shellac.

FDA advises that the devices listed above that are identified by a common docket number have been grouped. See the information under the heading "D. Grouping of Similar Devices—Withdrawal of 67 Dental Proposed Regulations Because of Different Grouping," earlier in this preamble.

4. Zinc oxide eugenol; Docket No. 78N-2913; proposed class II; § 872.3275; dental cement; proposed class II. Many comments recommended that zinc oxide eugenol be classified into class I because it has been used for a long time without any problems.

4a. Zinc oxide eugenol. FDA now believes that zinc oxide eugenol should be classified into class I. FDA proposed to classify the device into class II because of concerns about possible bioincompatibility of the device resulting in adverse tissue reactions. However, FDA now believes that in 1980, when it proposed to classify the device, the agency assigned to the device a higher level of risk of bioincompatibility than was justified by the years of experience of dentists and patients with the device. Thus, FDA now believes that it is unnecessary to establish a performance standard for zinc oxide eugenol to control the risk of bioincompatibility, because the device presents only minimal risks of bioincompatibility and that these minimal risks would not be significantly reduced through establishing a performance standard for the device due to the idiosyncratic nature of individual sensitivities. The labeling of a device that causes sensitivity reactions in some individuals should be so labeled to be in compliance with the misbranding provisions [21 U.S.C. 352] of the general controls of the act. FDA now believes that the general controls of class I alone would provide reasonable assurance of the safety and effectiveness of the device. Accordingly, FDA is classifying zinc oxide eugenol into class I.

4b. Dental cement. FDA proposed that dental cement, including zinc oxide eugenol dental cement, be classified into class II because materials used in the device should meet a generally accepted and satisfactory level of biocompatibility. FDA believes that a performance standard is necessary for dental cement other than zinc oxide eugenol, because general controls alone are insufficient to control the risks to health presented by this device. The agency believes that a performance standard would provide reasonable assurance of the safety and effectiveness of dental cement other than zinc oxide eugenol, and that sufficient information is available to establish a performance standard for dental cement other than zinc oxide eugenol.

Zinc oxide eugenol was identified in two proposed regulations (§ 872.3000, Docket No. 78N-2013 and § 872.3275, Docket No. 78N-2858). In the final rule, FDA is treating zinc oxide eugenol as a subtype of the generic type of device dental cement (§ 872.3275). Accordingly, FDA is classifying zinc oxide eugenol (including zinc oxide eugenol dental cement) into class I and classifying dental cement other than zinc oxide eugenol into class II.

5. Section 872.3700; Dental mercury; proposed class II. Comments recommended that dental mercury be classified into class I instead of class II as proposed. The comments acknowledged that elemental mercury is a poison, but stated that the risks to health presented to dentists and other dental workers are inherent in the device and would not be reduced through establishment of performance standards for the device. The comments also stated that manufacturers have voluntarily accomplished several actions to protect dentists and other dental workers from the inherent risks presented by the device, such as packaging the device in leak-proof containers and placing cautionary statements in the labeling of the device.

FDA agrees with comments urging that this device be classified into class I. As stated in the proposed regulation, FDA believes that presently there is no valid scientific evidence of systemic poisoning to patients exposed to amalgam containing mercury. FDA acknowledges that the device presents a risk to those few patients who experience allergic reactions to this material, as evidenced by rare reports of such reactions (Refs. 9, 10, and 11), and to individuals such as dentists who regularly handle dental mercury. Upon further consideration, FDA now believes that labeling for the device bearing adequate directions for use and warnings under the misbranding provisions [21 U.S.C. 352] of the general controls of the act would warn dentists about the rare risk of allergic reactions among patients and the risk of toxicity to dental health professionals. Establishing a performance standard for dental mercury would do nothing to reduce these risks. Thus, FDA believes that the general controls of class I alone are sufficient to provide reasonable assurance of the safety and effectiveness of the device and that it is unnecessary to establish performance standards for the device. Accordingly, FDA is classifying the device into class I.

6. Section 872.5550; Teething ring; proposed class I or class II depending upon the construction of the device. FDA received comments stating that (a) teething rings should not be considered a medical device, (b) problems with the use of teething rings do not exist, and (c) teething rings pose no hazards to health and, therefore, should be in class I.

FDA agrees in part and disagrees in part with these comments. With regard to the first comment, FDA has determined that it will regulate as medical devices only those teething rings (fluid-filled or solid) for which medical claims are made. Teething rings without medical claims are under the regulatory authority of the Consumer Product Safety Commission (CPSC). Most teething rings are not marketed with medical claims. Thus, the vast majority of teething rings are subject to the CPSC's jurisdiction rather than FDA's jurisdiction.

With regard to the second and third comments, FDA disagrees with the comments as applied to the fluid-filled version of this device. FDA proposed that the fluid-filled teething rings (such as one containing water) for which medical claims are made be classified into class II because FDA has received reports of microbial contamination of fluid-filled teething rings (Ref. 5). An infant who bites and ruptures a fluid-filled teething ring with contaminated contents could develop an infection. FDA continues to believe, therefore, that a performance standard is necessary to control risks to infant health if the fluid in the device is contaminated with microbes. Accordingly, FDA is classifying into class II fluid-filled teething rings for which medical claims are made.

FDA is classifying solid teething rings for which medical claims are made into class I, as proposed.

7. Section 872.4240; Rotary bone cutting handpiece; proposed class II: A comment noted that the rotary bone cutting handpiece is intended to operate at slower speeds than the regular "high speed" handpiece that FDA also

proposed to classify into class II. The comment suggested, therefore, that the rotary bone cutting handpiece should be classified into class I because it presents less risk to health than the "high speed" (air-powered) handpiece (78N-2918) and because the risk to health identified by the Panel, i.e., unnecessary trauma, cannot be controlled by a performance standard.

FDA disagrees with the comment. FDA believes that a performance standard is necessary for this device to assure that its design will not cause bone damage or tissue trauma and that the risk to health can be controlled by a performance standard. Accordingly, FDA is classifying the device into class II.

8. Section 872.4820; AC-powered bone saw; proposed class II: A comment stated that the AC-powered bone saw should be classified into class I because the risks to health identified by the Panel, i.e., the possibility of bone and tissue trauma and electrical shock, are not sufficient to warrant classification of the device into class II.

FDA disagrees with the comment. FDA believes that a performance standard is necessary for this device to assure that its design will not cause bone damage or tissue trauma. Accordingly, FDA believes that the proposed classification was correct and, therefore, is classifying the device into class II.

9. Comments on the proposed regulations classifying the devices listed below argued that the devices should be placed into class I because the agency identified no substantive risks to health associated with the devices that would justify classifying them into class II. The comments argued further that the biocompatibility concerns of the agency are unfounded and, therefore, that the statutory criteria for class II have not been met.

Section No.	Device	Class recommended by section	Class proposed by FDA
872.3310	Coating material for resin fillings	II	II
872.3590	Preformed plastic denture tooth	II	II
872.3690	Tooth shade resin material	II	II
872.3750	Bracket adhesive resin and tooth conditioner	II	II
872.3760	Denture relining, repairing, or rebasing resin	II	II
872.3765	Pit and fissure sealant and conditioner	I	II
872.3770	Temporary crown and bridge resin	I	II
872.3820	Root canal filling resin	I	II
872.5470	Orthodontic plastic bracket		

FDA disagrees with these comments. FDA believes that the biocompatibility and performance concerns discussed in the proposed regulations warrant classifying these devices into class II. There are numerous materials that may be used in these devices that could have an adverse effect on patients. For example, there are studies that describe the carcinogenic potential of certain materials that may be used to fabricate dental resins (Refs. 1 and 2). Because of the potentially serious risks that may be presented by exposure to various materials used in these devices, the agency believes that, except for a root canal filling resin containing chloroform, performance standards are necessary to provide reasonable assurance of the safety and effectiveness of these devices.

The agency has been informed that certain root canal filling resins in commercial distribution may contain chloroform as an ingredient. FDA believes that the safety and effectiveness of a root canal filling resin containing chloroform has not been established because chloroform may be a carcinogen. In the Federal Register of June 29, 1976 (41 FR 26842), FDA published a final rule declaring that any human drug or cosmetic product containing chloroform that is introduced or delivered for introduction in interstate commerce will be subject to regulatory action.

The agency believes that root canal filling resin containing chloroform presents a potential unreasonable risk of illness or injury because of possible carcinogenicity. Consequently, FDA now believes that premarket approval is necessary for root canal filling resin containing chloroform. FDA believes that general controls and performance standards are insufficient to provide reasonable assurance of the safety and effectiveness of this device when it contains chloroform and that insufficient information exists to establish a standard to provide such assurance.

Accordingly, except for root canal filling resin containing chloroform, FDA believes that the proposed classifications of the devices above are correct and is classifying the devices into class II. FDA is classifying root canal filling resin into class II when chloroform is not used as an ingredient and is classifying this device into class III when it contains chloroform.

10. The only specific comments received on the proposed classifications of the devices listed below agreed with FDA's proposals to classify the devices into class II. The comments stated that implantation of these devices may have undesirable effects on patients if improper materials are used in the devices' composition.

Docket No.	Device
78N-2888	Titanium subperiosteal implant material.
78N-2889	Cobalt chrome molybdenum implant material.

FDA agrees with the comments. For the reasons provided in the proposed regulations, FDA is classifying these devices into class II (§ 872.3645).

11. Comments on the proposed classifications of the devices listed below argued that the devices should be classified into class I rather than class II as proposed. The comments suggested that if the identifications of these devices were limited to devices of the same composition as those are being marketed with demonstrated acceptable levels of safety and effectiveness, the general controls provided by class I would be sufficient to assure their safety and effectiveness. In that case, the comments reasoned, a manufacturer intending to market a new device of this type or a device of a different composition would be required to submit to FDA a premarket notification, and FDA could place that device into a

class other than class I if it determined that class I was not sufficient to assure its safety or effectiveness.

Docket No.	Device	Class recommended by section	Class proposed by FDA
78N-2844	Gold based alloy for clinical use	II	II
78N-2845	Precious metal alloy for clinical use	II	II
78N-2851	Precision attachment	I	II
78N-2852	Preformed bar	I	II
78N-2858	Preformed clasp	I	II
78N-2860	Preformed wire clasp	II	II
78N-2849	Preformed anchor	I	II
78N-2863	Preformed crown	I	II
78N-2864	Gold and stainless steel cusp	I	II
78N-2865	Preformed cusp	I	II
78N-2884	Preformed gold denture tooth	I	II
78N-2898	Retentive and splinting pin	I	II
78N-2904	Root canal post	I	II
78N-2910	Posterior artificial teeth with metal insert	I	II

The Panel had recommended that gold based alloy for clinical use and precious metal alloy for clinical use be placed in class II in order to prevent an adverse tissue reaction if the materials used in the devices are not biocompatible. FDA still agrees with the Panel's recommendations on these two devices and, therefore, is classifying them into class II as proposed.

With respect to the classification of the other devices listed above, FDA agrees with the comments recommending that the devices be classified into class I rather than class II. The agency believes that each of these devices has maintained an acceptable level of performance based on the compositional range of the materials now being used in the devices; i.e., austenitic alloys or alloys of 75 percent or greater content of gold and metals of the platinum group. Devices of such composition have been shown to be biocompatible, inert, sufficiently strong, and otherwise safe and effective when used in the mouth. Consequently, considering that FDA will learn of new compositions of material, through premarket notification under section 510(k) of the act (21 U.S.C. 360(k)), FDA agrees that the general controls of class I are sufficient to provide reasonable assurance of the safety and effectiveness of these devices and that establishment of a performance standard for these devices is unnecessary. As suggested by the comments, FDA is changing the identification of each of these devices to state that the device is composed of austenitic alloys or alloys containing 75 percent or greater gold and metals of the platinum group.

12. Comments on the proposed regulations on the devices listed below argued that, because a performance standard administered by FDA under the Radiation Control for Health and Safety Act (42 U.S.C. 263f) already exists for each of these devices, establishing any additional performance standards under the amendments would be overregulation. The comments argued that the existing standards to which these devices are required to conform should be the sole standards for these devices.

Section	Device	Class recommended by section	Class proposed by FDA
872.1800	Extraoral source X-ray system	II	II
872.1810	Intraoral source X-ray system	II	II
872.1830	Cephalometer	II	II
872.1840	Dental X-ray position indicating device	II	II
872.1850	Lead-lined position indicator	II	II

When the only risk to health presented by a radiation-emitting device is adequately controlled by a standard under the Radiation Control and Safety Act, no other standard is needed to assure the safety and effectiveness of a medical device, and FDA will classify the device into class I. However, the devices listed above present risks to health other than those controlled by an existing standard. For example, unintended exposure to x-rays resulting from lack of effectiveness due to faulty design of the device may not be covered by an existing standard but may need to be controlled by a performance standard under section 514 of the act (21 U.S.C. 360d) to assure a device's safety and effectiveness. Accordingly, FDA is classifying each of the devices listed above into class II as proposed.

13. Comments on the proposed regulations classifying the devices listed below argued that these devices are raw materials used in the fabrication of custom devices and, therefore, should be exempt from sections 514 and 515 of the act (21 U.S.C. 360d and 360e) under the custom device exemption in section 520(b) of the act (21 U.S.C. 360j(b)). The comments further stated that none of these devices is intended for use by a patient until it is tailored by a trained professional to meet the individual needs of the patient.

Section	Device
872.1730	Electrode gel for pulp tester.
872.3050	Amalgam alloy.
872.3060	Gold based alloy for clinical use.
872.3250	Calcium hydroxide cavity liner
872.3260	Cavity varnish.
872.3275	Dental cement.

Section	Device
872.3300	Hydrophilic resin coating for dentures.
872.3310	Coating material for resin linings.
872.3690	Preformed plastic denture tooth.
872.3650	Impression material.
872.3700	Dental mercury.
872.3710	Base metal alloy.
872.3750	Bracket adhesive resin and tooth conditioner.
872.3760	Denture relining, repairing, or rebasing resin.
872.3765	Pit and fissure sealant and conditioner.
872.3850	Gutta percha.
872.3920	Porcelain tooth.
872.5410	Orthodontic preformed band.
872.6660	Porcelain powder for clinical use.
872.6090	Intraoral dental wax.

FDA disagrees with the comments. The devices listed above do not meet the requirements of the partial exemption for custom devices because (a) the devices need not necessarily deviate from an otherwise applicable performance standard or requirement prescribed by or under section 515 of the act, (b) the devices are generally available in finished form for purchase or for dispensing upon prescription, (c) the devices are offered for commercial distribution, and (d) the devices are generally available to or generally used by dentists. Thus, although these devices may be formed according to the needs of individual patients, the devices do not meet the requirements of section 520(b) of the act for an exemption from section 514 or 515.

14. Comments on the proposed regulations listed below argued that, in classifying these devices, both the Panel and FDA incorrectly used the criteria that were used by FDA's OTC Drug Review Panel in its review of these products when they were regarded as drugs. The comments argued that the criteria used for classifying devices should be different from those applied by the OTC Drug Review Panel. The comments also suggested that the devices be classified into class I, rather than class III as proposed, because of insufficient documentation that they present an actual risk to users.

Section	Device	Class recommended by section	Class proposed by FDA
872.3540	OTC denture cushion	III	III
872.3550	OTC denture pad	III	III
872.3560	OTC denture reliner	III	III
872.3570	OTC denture repair kit	III	III

FDA agrees in part and disagrees in part with the comments. FDA disagrees that the agency employed incorrect criteria when proposing to classify these devices. As stated in the proposals, the devices present a risk of illness or injury. Use of these devices may cause an improper vertical dimension of a denture which may result in increased biting forces and lead to bone loss through resorption (degeneration of the bone through gradual dissolution). The long-term irritation of oral tissue caused by an incorrect vertical dimension also could cause formation of carcinomas. FDA also disagees with the comments' assertion that FDA did not provide in the proposed regulations sufficient documentation of the health risks presented by these devices. FDA cited in the proposed regulations a summary report by the OTC Panel on Dentifrices and Dental Care Agents, May 22, 1978, showing the hazards presented by these devices (Ref. 6).

Section 872.3540; OTC denture cushion: During an open meeting of the Panel on March 12 and 13, 1979, a manufacturer presented the results of a study that showed that disposable OTC denture cushions made of wax-impregnated cotton cloth that the patient applies to the entire base of a denture before the patient inserts the denture into the mouth are safe and effective for short-term use (Ref. 7). The Panel believed that the data showed that this version of the OTC denture cushion is safe and effective; because a single layer of material is used to make the cushion, the disposable cushion is discarded after 1 day's use, and the device is intended for short-term use. Therefore, during that meeting, the Panel recommended that this version of the OTC denture cushion be classified into class I. Inadvertently, FDA did not reflect this portion of the Panel's recommendation in its proposed classifications of the OTC denture cushion and OTC denture pad. A summary of the Panel's recommendation is, however, in the administrative record for this rulemaking. FDA agrees with the recommendations of the Panel that the OTC denture cushion be classified into class I, provided that the device is made of wax-impregnated cotton cloth and is for the intended uses described above.

In the final rule, FDA has grouped the OTC denture cushion and the OTC denture pad into one generic type of device, the OTC denture cushion and pad (§ 872.3540).

Accordingly, in the final rule FDA is classifying into class I the OTC denture cushion and pad, if the device is made of wax-impregnated cotton cloth, if it is intended to be discarded after 1 day's use, and if it is intended for short-term use. FDA is classifying all other OTC denture cushions and pads, the OTC denture reliner, and the OTC denture repair kit into class III as proposed. FDA is classifying these devices into class III because these devices present potential unreasonable risks of illness or injury as described above and in the proposals, and because general controls or performance standards are insufficient to provide reasonable assurance of their safety and effectiveness.

15. Comments on the proposed regulations classifying the denture adhesives listed below said that these devices should not be identified by the names of the ingredients in them. The comments said that, by listing the specific ingredients or precentages of ingredients in the names of these devices and in their identifications, FDA is inhibiting formula improvements by subjecting denture adhesives containing different ingredients or different percentages of ingredients to extensive compliance requirements, such as submission of premarket notification and petitions for reclassification.

Docket No.	Device
76N-2666	Acacia and Karaya with sodium borate denture adhesive.
76N-2667	Carboxymethylcellulose sodium (40 to 100 percent) denture adhesive.
76N-2668	Carboxymethylcellulose sodium and cationic polyacrylamide polymer denture adhesive.
76N-2669	Carboxymethylcellulose sodium (32 percent) and ethylene oxide homopolymer (13 percent) denture adhesive.
76N-2670	Carboxymethylcellulose sodium (49 percent) and ethylene oxide homopolymer (21 percent) denture adhesive.
76N-2671	Karaya denture adhesive.
76N-2672	Karaya and ethylene oxide homopolymer denture adhesive.

Authority: Secs. 501(f), 510, 513, 515, 520, 701(a), 52 Stat. 1055, 76 Stat. 794–795 as amended, 90 Stat. 540–546, 552–559, 565–574, 576–577 (21 U.S.C. 351(f), 360, 360c, 360e, 360j, 371(a)); 21 CFR 5.10.

Subpart A—General Provisions

§ 872.1 Scope.

(a) This part sets forth the classification of dental devices intended for human use that are in commercial distribution.

(b) The identification of a device in a regulation in this part is not a precise description of every device that is, or will be, subject to the regulation. A manufacturer who submits a premarket notification submission for a device under Part 807 cannot show merely that the device is accurately described by the section title and identification provisions of a regulation in this part, but shall state why the device is substantially equivalent to other devices, as required by § 807.87.

(c) To avoid duplicative listings, a dental device that has two or more types of uses (e.g., used both as a diagnostic device and as a therapeutic device) is listed in one subpart only.

(d) References in this part to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 872.3 Effective dates of requirement for premarket approval.

A device included in this part that is classified into class III (premarket approval) shall not be commercially distributed after the date shown in the regulation classifying the device unless the manufacturer has an approval under section 515 of the act (unless an exemption has been granted under section 520(g)(2) of the act). An approval under section 515 of the act consists of FDA's issuance of an order approving an application for premarket approval (PMA) for the device or declaring completed a product development protocol (PDP) for the device.

(a) Before FDA requires that a device commercially distributed before the enactment date of the amendments, or a device that has been found substantially equivalent to such a device, has an approval under section 515 of the act, FDA must promulgate a regulation under section 515(b) of the act requiring such approval, except as provided in paragraphs (b) and (c) of this section. Such a regulation under section 515(b) of the act shall not be effective during the grace period ending on the 90th day after its promulgation or on the last day of the 30th full calendar month after the regulation that classifies the device into class III is effective, whichever is later. See section 501(f)(2)(B) of the act. Accordingly, unless an effective date of the requirement for premarket approval is shown in the regulation for a device classified into class III in this part, the device may be commercially distributed without FDA's issuance of an order approving a PMA or declaring completed a PDP for the device. If FDA promulgates a regulation under section 515(b) of the act requiring premarket approval for a device, section 501(f)(1)(A) of the act applies to the device.

(b) Any new, not substantially equivalent, device introduced into commercial distribution on or after May 28, 1976, including a device formerly marketed that has been substantially altered, is classified by statute (section 513(f) of the act) into class III without any grace period and FDA must have issued an order approving a PMA or declaring completed a PDP for the device before the device is commercially distributed unless it is reclassified. If FDA knows that a device being commercially distributed may be a "new" device as defined in this section because of any new intended use or other reasons, FDA may codify the statutory classification of the device into class III for such new use. Accordingly, the regulation for such a class III device states that as of the enactment date of the amendments, May 28, 1976, the device must have an approval under section 515 of the act before commercial distribution.

(c) A device identified in a regulation in this part that is classified into class III and that is subject to the transitional provisions of section 520(l) of the act is automatically classified by statute into class III and must have an approval under section 515 of the act before being commercially distributed. Accordingly, the regulation for such a class III transitional device states that as of the enactment date of the amendments, May 28, 1976, the device must have an approval under section 515 of the act before commercial distribution.

Subpart B—Diagnostic Devices

§ 872.1500 Gingival fluid measurer.

(a) *Identification.* A gingival fluid measurer is a gauge device intended to measure the amount of fluid in the gingival sulcus (depression between the tooth and gums) to determine if there is a gingivitis condition.

(b) *Classification.* Class I.

§ 872.1720 Pulp tester.

(a) *Identification.* A pulp tester is an AC or battery powered device intended

to evaluate the pulpal vitality of teeth by employing high frequency current transmitted by an electrode to stimulate the nerve tissue in the dental pulp.

(b) *Classification.* Class II.

§ 872.1730 Electrode gel for pulp testers.

(a) *Identification.* An electrode gel for pulp testers is a device intended to be applied to the surface of a tooth before use of a pulp tester to aid conduction of electrical current

(b) *Classification.* Class I.

§ 872.1740 Caries detection device.

(a) *Identification.* The caries detection device is a device intended to show the existence of decay in a patient's tooth by use of electrical current.

(b) *Classification.* Class II.

§ 872.1800 Extraoral source X-ray system.

(a) *Identification.* An extraoral source X-ray system is an AC-powered device that produces X-rays and is intended for dental radiographic examination and diagnosis of diseases of the teeth, jaw, and oral structures. The X-ray source (a tube) is located outside the mouth. This generic type of device may include patient and equipment supports and component parts.

(b) *Classification.* Class II.

§ 872.1810 Intraoral source X-ray system.

(a) *Identification.* An intraoral source X-ray system is an electrically powered device that produces X-rays and is intended for dental radiographic examination and diagnosis of diseases of the teeth, jaw, and oral structures. The X-ray source (a tube) is located inside the mouth. This generic type of device may include patient and equipment supports and component parts.

(b) *Classification.* Class II.

§ 872.1820 Dental X-ray exposure alignment device.

(a) *Identification.* A dental X-ray exposure alignment device is a device intended to position X-ray film and to align the examination site with the X-ray beam.

(b) *Classification.* Class I.

§ 872.1830 Cephalometer.

(a) *Identification.* A cephalometer is a device used in dentistry during X-ray procedures. The device is intended to place and to hold a patient's head in a standard position during dental X-rays.

(b) *Classification.* Class II.

§ 872.1840 Dental X-ray position indicating device.

(a) *Identification.* A dental X-ray position indicating device is a device, such as a collimator, cone, or aperture, that is used in dental radiographic examination. The device is intended to align the examination site with the X-ray beam and to restrict the dimensions of the dental X-ray field by limiting the size of the primary X-ray beam.

(b) *Classification.* Class II.

§ 872.1850 Lead-lined position indicator.

(a) *Identification.* A lead-lined position indicator is a cone-shaped device lined with lead that is attached to a dental X-ray tube and intended to aid in positioning the tube, to prevent the misfocusing of the X-rays by absorbing divergent radiation, and to prevent leakage of radiation.

(b) *Classification.* Class II.

§ 872.1905 Dental X-ray film holder.

(a) *Identification.* A dental X-ray film holder is a device intended to position and to hold X-ray film inside the mouth.

(b) *Classification.* Class I. If the device is not labeled or otherwise represented as sterile, it is exempt from the current good manufacturing practice regulations in Part 820, with the exception of § 820.180, with respect to general requirements concerning records, and § 820.198 with respect to complaint files.

Subpart C—[Reserved]

Subpart D—Prosthetic Devices

§ 872.3050 Amalgam alloy.

(a) *Identification.* An amalgam alloy is a device that consists of a metallic substance intended to be mixed with mercury to form filling material for treatment of dental caries.

(b) *Classification.* Class II.

§ 872.3060 Gold-based alloys and precious metal alloys for clinical use.

(a) *Identification.* Gold-based alloys and precious metal alloys for clinical use are mixtures of metals, the major components of which are gold, silver, or palladium. They also may contain a small quantity of copper or platinum. The device is intended to fabricate dental appliances, such as crowns and bridges, for patients.

(b) *Classification.* Class II

§ 872.3080 Mercury and alloy dispenser.

(a) *Identification.* A mercury and alloy dispenser is a device with a spring-activated valve intended to measure and dispense into a mixing capsule a predetermined amount of dental mercury in droplet form and a premeasured amount of alloy pellets.

(b) *Classification.* Class I.

§ 872.3110 Dental Amalgam capsule.

(a) *Identification.* A dental amalgam capsule is a container device in which silver alloy is intended to be mixed with mercury to form dental amalgam.

(b) *Classification.* Class I.

§ 872.3130 Preformed anchor.

(a) *Identification.* A preformed anchor is a device made of austenitic alloys or alloys containing 75 percent or greater gold or metals of the platinum group intended to be incorporated into a dental appliance, such as a denture, to help stabilize the appliance in the patient's mouth.

(b) *Classification.* Class I.

§ 872.3140 Resin applicator.

(a) *Identification.* A resin applicator is a brushlike device intended for use in spreading dental resin on a tooth during application of tooth shade material.

(b) *Classification.* Class I. If the device is not labeled or otherwise represented as sterile, it is exempt from the current good manufacturing practice regulations in Part 820, with the exception of § 820.180, with respect to general requirements concerning records, and § 820.198, with respect to complaint files.

§ 872.3150 Articulator.

(a) *Identification.* An articulator is a mechanical device intended to simulate movements of a patient's upper and lower jaws. Plaster casts of the patient's teeth and gums are placed in the device to reproduce the occlusion (bite) and articulation of the patient's jaws. An articulator is intended to fit dentures or provide orthodontic treatment.

(b) *Classification.* Class I. If the device is not labeled or otherwise represented as sterile, it is exempt from the current good manufacturing practice regulations in Part 820, with the exception of § 820.180, with respect to general requirements concerning records, and § 820.198, with respect to complaint files.

§ 872.3165 Precision attachment.

(a) *Identification.* A precision attachment of preformed bar is a device made of austenitic alloys or alloys containing 75 percent or greater gold and metals of the platinum group intended for use in prosthetic dentistry in conjunction with removable partial dentures. Various forms of the device are intended to connect a lower partial denture with another lower partial denture, to connect an upper partial denture with another upper partial denture, to connect either an upper or lower partial denture to a tooth or a

artificial teeth, and to restore the patient's chewing function.

(b) *Classification.* Class III.

(c) *Date PMA or notice of completion of a PDP is required:* No effective date has been established of the requirement for premarket approval. See § 872.3.

§ 872.3645 Subperiosteal implant material.

(a) *Identification.* Subperiosteal implant material is a device composed of titanium or cobalt-chrome molybdenum intended to construct custom prosthetic devices which are surgically implanted into the lower or upper jaw between the periosteum (connective tissue covering the bone) and supporting bony structures. The device is intended to provide support for prostheses, such as dentures.

(b) *Classification.* Class II.

§ 872.3660 Impression material.

(a) *Identification.* Impression material is a device composed of materials such as alginate or polysulfide intended to be placed on a preformed impression tray and used to reproduce the structure of a patient's teeth and gums. The device is intended to provide models for study and for production of restorative prosthetic devices, such as gold inlays and dentures.

(b) *Classification.* Class II.

§ 872.3670 Resin impression tray material.

(a) *Identification.* Resin impression tray material is a device intended for use in a two-step dental mold fabricating process. The device consists of a resin material, such as methyl methacrylate, and is used to form a custom impression tray for use in cases in which a preformed impression tray is not suitable, such as the fabrication of crowns, bridges, or full dentures. A preliminary plaster or stone model of the patient's teeth and gums is made. The resin impression tray material is applied to this preliminary study model to form a custom tray. This tray is then filled with impression material and inserted into the patient's mouth to make an impression, from which a final, more precise, model of the patient's mouth is cast.

(b) *Classification.* Class I. If the device is not labeled or otherwise represented as sterile, it is exempt from the current good manufacturing practice regulations in Part 820, with the exception of § 820.180, with respect to general requirements concerning records, and § 820.198, with respect to complaint files.

§ 872.3680 Polytetrafluoroethylene (PTFE) vitreous carbon materials.

(a) *Identification.* Polytetrafluoroethylene (PTFE) vitreous carbon material is a device composed of polytetrafluoroethylene (PTFE) vitreous carbon intended for use in maxillofacial alveolar ridge augmentation (building up the upper or lower jaw area that contains the sockets in which teeth are rooted) or intended to cost metal surgical implants to be placed in the alveoli (sockets in which the teeth are rooted) or the temporomandibular joints (the joint between the upper and lower jaws).

(b) *Classification.* Class II.

§ 872.3690 Tooth shade resin material.

(a) *Identification.* Tooth shade-resin material is a device composed of materials such as bisphenol-A glycidyl methacrylate (Bis-GMA) intended to restore carious lesions or structural defects in teeth.

(b) *Classification.* Class II.

§ 872.3700 Dental mercury.

(a) *Identification.* Dental mercury is a device composed of mercury intended for use as a component of amalgam alloy in the restoration of a dental cavity or a broken tooth.

(b) *Classification.* Class I.

§ 872.3710 Base metal alloy.

(a) *Identification.* A base metal alloy is a device composed of a material, such as a mixture of nickel and chromium, intended for use in fabrication of a custom-made dental device, such as porcelain veneer for a tooth.

(b) *Classification.* Class II.

§ 872.3730 Pantograph.

(a) *Identification.* A pantograph is a device intended to be attached to a patient's head to duplicate lower jaw movements to aid in construction of restorative and prosthetic dental devices. A marking pen is attached to the lower jaw component of the device and, as the patient's mouth opens, the pen records on graph paper the angle between the upper and the lower jaw.

(b) *Classification.* Class I. The device is exempt from the premarket notification procedures in Subpart E of Part 807. If the device is not labeled or otherwise represented as sterile, it is exempt from the current good manufacturing practice regulations in Part 820, with the exception of § 820.180, with respect to general requirements concerning records, and § 820.198, with respect to complaint files.

§ 872.3740 Retentive and splinting pin.

(a) *Identification.* A retentive and splinting pin is a device made of austenitic alloys or alloys containing 75 percent or greater gold and metals of the platinum group intended to be placed permanently in a tooth to provide retention and stabilization for a restoration, such as a crown, or to join two or more teeth together.

(b) *Classification.* Class I.

§ 872.3750 Bracket adhesive resin and tooth conditioner.

(a) *Identification.* A bracket adhesive resin and tooth conditioner is a device composed of an adhesive compound, such as polymethylmethacrylate, intended to cement an orthodontic bracket to a tooth surface.

(b) *Classification.* Class II.

§ 872.3760 Denture relining, repairing, or rebasing resin.

(a) *Identification.* A denture relining, repairing, or rebasing resin is a device composed of materials such as methylmethacrylate, intended to reline a denture surface that contacts tissue, to repair a fractured denture, or to form a new denture base. This device is not available for over-the-counter (OTC) use.

(b) *Classification.* Class II.

§ 872.3765 Pit and fissure sealant and conditioner.

(a) *Identification.* A pit and fissure sealant and conditioner is a device composed of resin, such as polymethylmethacrylate, intended for use primarily in young children to seal pit and fissure depressions (faults in the enamel) in the biting surfaces of teeth to prevent cavities.

(b) *Classification.* Class II.

§ 872.3770 Temporary crown and bridge resin.

(a) *Identification.* A temporary crown and bridge resin is a device composed of a material, such as polymethylmethacrylate, intended to make a temporary prosthesis, such as a crown or bridge, for use until a permanent restoration is fabricated.

(b) *Classification.* Class II.

§ 872.3810 Root canal post.

(a) *Identification.* A root canal post is a device made of austenitic alloys or alloys containing 75 percent or greater gold and metals of the platinum group intended to be cemented into the root canal of a tooth to stabilize and support a restoration.

(b) *Classification.* Class I.

§ 872.3820 Root canal filling resin.

(a) *Identification.* A root canal filling resin is a device composed of material, such as methylmethacrylate, intended for use during endodontic therapy to fill the root canal of a tooth.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 872

[Docket No. 78N-2830 et al.]

Medical Devices; Withdrawal of 67 Proposed Rules Classifying Dental Devices

AGENCY: Food and Drug Administration.

ACTION: Withdrawal of proposed rules.

SUMMARY: The Food and Drug Administration (FDA) is withdrawing 67 proposed rules in the classification of dental devices to avoid unnecessary regulations. Elsewhere in this issue of the Federal Register, FDA is publishing a final rule classifying 110 dental devices.

FOR FURTHER INFORMATION CONTACT: Gregory Singleton, Center for Devices and Radiological Health (HFZ-470), Food and Drug Administration, 8757 Georgia Ave., Silver Spring, MD 20910, 301-427-7555.

SUPPLEMENTARY INFORMATION: In the Federal Register of December 30, 1980 (45 FR 85992-86168), FDA proposed to classify 185 dental devices. This action was taken as part of the agency's overall implementation of the Medical Device Amendments of 1976 (the amendments) that established a system for the regulation of medical devices for human use. One provision of the amendments, section 513 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360c), establishes three categories (classes) of devices, depending on the regulatory controls needed to provide reasonable assurance of their safety and effectiveness: Class I (general controls), class II (performance standards), and class III (premarket approval). The amendments also established a procedure for the agency to promulgate regulations classifying each generic type of device into one of these three classes. Persons who disagree with a final classification of a device may petition for reclassification of the device under Subpart C of 21 CFR Part 860. Because the same generic type of device may be used in different medical specialty areas (cardiovascular, general and plastic surgery, anesthesiology, etc.) under different names, and because FDA is attempting to eliminate unnecessary regulations, the agency continues to consolidate its list of generic types of devices.

FDA is withdrawing 67 of the 185 dental proposed regulations that were published on December 30, 1980. Elsewhere in this issue of the Federal Register, FDA is publishing a final rule classifying dental devices. In that final rule, FDA is grouping 69 proposed dental devices into 22 generic types of dental devices. The term "generic type of device" is defined in 21 CFR 860.3(i). Therefore, in that final rule each of the 67 proposed devices listed below in the left column is being grouped into the generic type of device opposite in the right column. FDA is withdrawing each of the proposed regulations listed in the left column. FDA advises that summaries of any comments submitted on the 67 proposed regulations being withdrawn and FDA's responses to these comments are discussed in the final rule classifying dental devices that is being published elsewhere in this issue of the Federal Register. Further, as explained in that final rule, FDA is not publishing at this time classifications of certain dental devices, including 10 devices listed below, i.e., those numbered 58 through 67, for which proposals are being withdrawn. Classifications of the devices in the right column opposite the proposals numbered 58 through 67 are not being classified by FDA now.

Proposed regulations being withdrawn		Elsewhere in this issue of the Federal Register, FDA is publishing final regulations classifying these devices
1. 78N-2845	Precious metal alloy for clinical use	78N-2844 Gold based alloys and precious metal alloys for clinical use.
2. 78N-2852	Preformed bar	78N-2851 Precision attachment.
3. 78N-2913	Zinc oxide eugenol	78N-2858 Dental cement.
4. 78N-2860	Preformed wire clasp	78N-2859 Preformed clasp.
5. 78N-2873	Karaya with sodium borate denture adhesive	78N-2866 Karaya and/or acacia with 12 percent or less sodium borate denture adhesive
6. 78N-2868	Carboxymethylcellulose sodium (32%) and ethylene oxide homopolymer (13%) denture adhesive.	78N-2867 Ethylene oxide homopolymer and/or carboxymethyl-cellulose sodium denture adhesive.
7. 78N-2870	Carboxymethylcellulose sodium (49%) and ethylene oxide homopolymer (21%) denture adhesive.	Do.
8. 78N-2872	Karaya and ethylene oxide homopolymer denture adhesive	78N-2871 Ethylene oxide homopolymer and/or karaya denture adhesive.
9. 78N-2877	Polyvinylmethylether maleic acid calcium-sodium double salt and carboxymethyl-cellulose sodium denture adhesive.	78N-2875 Carboxymethylcellose sodium and/or polyvinylmethylether maleid acid calcium-sodium double salt denture adhesive.
10. 78N-2881	OTC denture pad	78N-2880 OTC denture cushion or pad.
11. 78N-2886	Cobalt chrome molybdenum subperiosteal implant material	78N-2888 Subperiosteal implant material.
12. 78N-2917	Powered bone drill	78N-2915. Bone cutting instruments and accessories.
13. 78N-2920	Rotary bone cutting handpiece	Do.
14. 78N-2941	AC-powered bone saw	Do.
15. 78N-3027	Endodontic broach	78N-2931 Dental hand instrument.
16. 78N-2914	Dental wax carver	Do.
17. 78N-3026	Endodontic pulp canal file	Do.
18. 78N-2927	Hand instruments for calculus removal	Do.
19. 78N-2928	Dental depth gauge instrument	Do.
20. 78N-2930	Plastic dental filling instrument	Do.
21. 78N-2932	Dental instrument handle	Do.
22. 78N-2945	Surgical tissue scissors	Do.
23. 78N-2952	Orthodontic band driver	Do.
24. 78N-2954	Orthodontic band pusher	Do.
25. 78N-2955	Orthodontic band setter	Do.
26. 78N-2958	Orthodontic bracket aligner	Do.
27. 78N-2962	Orthodontic pliers	Do.
28. 78N-2967	Orthodontic ligature tucking instrument	Do.
29. 78N-2990	Forceps for articulation paper	Do.
30. 78N-2991	Forceps for dental dressing	Do.
31. 78N-2997	Dental matrix band	Do.
32. 78N-2998	Matrix retainer	Do.
33. 78N-3000	Mouth mirror	Do.
34. 78N-3007	Dental retractor	Do.
35. 78N-3008	Dental retractor accessories	Do.
36. 78N-3018	Periodontic or endodontic irrigating syringe	Do.
37. 78N-3017	Restorative or impression material syringe	Do.
38. 78N-2938	Surgical highlight	78N-2935 Dental operating light.
39. 78N-2948	Intraosseous fixation wire	78N-2946 Intraosseous fixation screw or wire.
40. 78N-2950	Orthodontic elastic band	78N-2951 Orthodontic appliance and accessories.
41. 78N-2953	Orthodontic band material	Do.

DOCKET NO. 78N-2843, PROPOSED RULES, Dec 30, 1980

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

Ex.8

APR 2 1991

Duane E. Christian, D.M.D.
810 North Nevada Street
Carson City, Nevada 89701

Dear Dr. Christian:

Your letters of February 11, 1991, to Secretary Louis Sullivan and FDA Commissioner David Kessler have been referred to me for response. I apologize for the delay but, as you know, we have been preparing for the March 15 meeting of the Dental Products Panel. The delay is advantageous, however, in that the meeting has now taken place and I can provide you with specific information about the conduct of the meeting and the resolution of some of your concerns.

As you have observed, the Dental Products Panel described in your January 24, 1991, enclosure consists primarily of dental practioners and academicians, who may not be as conversant with the medical aspects of mercury toxicity as some researchers. However, you should recognize that this advisory panel is a standing committee, constituted to review a wide array of dental drugs and devices, of which dental amalgam is just one example.

To gain the specialized knowledge necessary to render recommendations on any given device, the panel relies on scientific input from outside consultants, invited speakers and FDA staff, and from others who ask to address the panel during the open public hearing at the meeting. Further, under a recently revised charter, we can supplement the membership of any panel with members from other medical device advisory panels. For the March 15 panel meeting, we supplemented the membership with members from four other medical device panels. We also attempted to provide a broad spectrum of speakers to cover all aspects and perspectives of the issue. Attached is a listing of the panel membership and invited speakers for the March 15 meeting.

The November ADA News story regarding Dr. Singleton's remarks about the Calgary research was an exaggeration of his actual statements. There were, in fact, flaws in the study, but the study was still worthwhile in many respects, as was stated by Dr. Singleton in that same interview. The fact that Dr. Singleton identified flaws should not be construed as evidence of a prejudicial attitude on the safety of amalgam.

Your concern that Dr. John Stanford is the chairman of the FDA Classification Panel on Dental Devices is unwarranted. The panel you identified as the FDA Classification Panel is the same panel identified in the January 24, 1991, enclosure to your letter as the Dental Products Panel. Dr. Stanford has not been the chairman in many years. The membership rotates and the current acting chairman is Dr. Duncanson. Dr. Stanford has been retained as a consultant to the panel.

Lastly, I want to address an apparent concern of yours, as discussed in the Bio-Probe Newsletter (September 1989), which you enclosed. You find fault in FDA's practice of not certifying mixed dental amalgam. Aside from the semantics issue (FDA does not certify any product), I must remind you that FDA regulates manufacturers of medical devices. No manufacturer produces mixed dental amalgams. The mixed dental amalgam is prepared by dental clinicians. FDA does regulate manufacturers of dental mercury and amalgam alloys, but the only control FDA has over the ultimate, mixed amalgam is through the labeling for dental mercury and amalgam alloys. The Federal Food, Drug, and Cosmetic Act does not empower FDA to regulate the manner in which dental clinicians mix dental mercury and amalgam alloys to make dental amalgams.

As I mentioned, the panel meeting has now taken place. I've enclosed for your information copies of some of the materials available at the meeting. I've also enclosed a copy of an FDA talk paper issued after the meeting. If you have any further concerns, please let me know. I may be reached at (301)427-1180 or you may write to me at the above address.

Sincerely yours,

Lillian Yin

Lillian Yin, Ph.D.
Director
Division of Ob-Gyn, ENT,
and Dental Devices
Office of Device Evaluation

Enclosures

Ex. 9

American Dental Trade Association

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FISE

STATEMENT

of the

AMERICAN DENTAL TRADE ASSOCIATION

to the

FDA Dental Products Panel

Presented by

John W. Stanford, Ph.D.
accompanied by
Nikolaj M. Petrovic, ADTA President
Thomas F. Fise, ADTA Special Counsel, Regulatory Affairs

RE: UPDATE REPORT: DENTAL AMALGAMS

December 3, 1993

UPDATE REPORT: DENTAL AMALGAMS

My name is John W. Stanford, Ph.D., and I appear here today on behalf of the American Dental Trade Association. ADTA is an international organization, and is the oldest and largest trade association representing the dental industry in the United States. ADTA has been in continuous operation since 1882 and its membership consists of dental distributors, the Dental Laboratory Conference (leading dental laboratories), and dental manufacturers. The volume of dental business represented by ADTA member companies amounts to distributors (85%); dental laboratories (65%); and manufacturers (70%). I am accompanied here today by Nikolaj M. Petrovic, ADTA's President and Chief Executive Officer, and Thomas Fise, ADTA's Special Counsel on Regulatory Affairs.

We appreciate the opportunity to make this presentation and to provide the Panel with an update report relating to dental amalgam. On March 15, 1991, the Dental Products Panel met after reviewing a vast amount of medical and scientific literature addressing human exposure to mercury from dental amalgam and resulting health impacts. The Panel considered testimony from U.S. and foreign experts as well as clinicians, patients, the American Dental Association and the National Institute for Dental Research. Included was a presentation by Dr. John Osbourne and Mr. Robert Pinco on behalf of several manufacturers of dental amalgam. After a careful consideration of all of the medical and scientific literature presented, as well as the detailed comments, the Panel concluded that none of the data showed a direct hazard to human health from dental amalgams. However, the Panel agreed that the studies presented did raise questions that warrant further research. The Panel recommended that the FDA establish a special working group to identify the kinds of animal and human studies needed to address certain questions and that this group should work in collaboration with other research organizations such as the National Institute for Dental Research (NIDR).

[Cite: FDA Talk Paper, March 20, 1991.]

In response to the March, 1991 finndings of the Dental Products Panel, the ADTA and several amalgam manufacturers immediately took action to implement the Panel's recommendations to work with NIDR and other health agencies to consider and implement appropriate research. This group carefully reviewed the Panel's technical and medical findings, talked at length with NIDR officals and scientific personnel, and endeavored to develop the requested research protocols to collect scientific information in the most objective and expeditious manner. A special fund was established within the American Fund for Dental Health, supported by amalgam manufacturers, for the purpose of supporting research contemplated by FDA and NIDR. Funding has been extended through the American Fund for Dental Health for a major comprehensive

longitudinal study where a component on dental amalgam has been factored into a comprehensive health history study on a cohort of Vietnam veterans. The research and epidemiology officials at the NIDR have been most positive about the potential value of this project, and we look forward to its completion (date being determined from Jack Brown at NIDR). Epidemiologist and other scientific staff at NIDR have viewed this project as a significant step in implementing the Dental Products Panel's research related recommendations.

In response to concerns raised by some members of the public on health effects from exposure to mercury and dental amalgam, the National Institutes of Health and the National Institute of Dental Research convened an NIH Technology Assessment Conference in August, 1991. This conference brought together dentists, toxicologists, biomaterial scientists and other medical specialists to review the properties, effects and side-effects of dental restorative materials in current use, including amalgams. Following 1-1/2 days of presentations and a full discussion by the audience, the Panel concluded:

> **"There is a little evidence that tooth restorative materials induce systemic toxicity. Elemental mercury can be released from amalgams, and mercury can be found in the brains and kidneys of humans and animals. However, except for dental personnel who have had excessive exposure due to repeated mishandling, altered brain or kidney function has not been correlated with dental amalgam exposure. Confirmed fetal effects from the use of dental amalgam have not been reported.**
>
> Very few patients appear to be at risk of developing a local toxic or allergic reaction in response to the placement of restorations. Even when such reactions occur, they may not cause a significant clinical effect.
>
> Current restorative materials can be used effectively for restoring teeth for functional or esthetics reasons. Virtually all restorative materials have components with potential health risks. However, there is no scientific evidence that currently used restorative materials cause significant side effects. Available data does not justify discontinuing the use of any currently available materials or recommending their replacement.
>
> Although mercury vapor is released from dental amalgam, the quantities released are very small and do not cause verifiable adverse effects on human beings.
>
> [Cite: Statement: Effects and Side Effects of Dental Restorative Materials, presented at the NIH Technology Assessment Conference on Effects and Side Effects of Dental Restorative Materials, August 26-28, 1991, National Institutes of Health, Bethesda, MD.]

Over the past two years, organizations around the wo exhaustively reviewed the voluminous medical and sci literature which addresses the potential for adverse effects from dental amalgam. Each and every one o organizations has concluded that there is no credible supp the proposition that dental amalgam poses any unnecessary risks to patients.

> "...extensive reviews of the scientific literature hav revealed any data published in refereed scientific jou to support claims that amalgam restorations have cause adverse biological reactions other than extremely allergy to one of the amalgam components."
>
> [Cite: Federation Dentaire Internationale, London, M 1992.]
>
> "Mercury released from dental amalgam does not, according available data, contribute to systemic disease or syste toxicological effects.
>
> No significant effects on the immune system have b demonstrated with the amounts of mercury which may released from dental amalgam fillings.
>
> There is no data supporting that mercury released fr dental amalgam gives rise to teratological effects."
>
> [Cite: Swedish Medical Research Council, April, 1992.]
>
> "Based on the available research, the NIDR concludes tha dental amalgams pose no known health risks to individual who are not hypersensitive to the materials."
>
> [Cite: Dr. Harald Loe, Director, U.S. National Institute o Dental Research]

For over two years, scientists and public health experts from the U.S. Public Health Service (PHS), the Environmental Protection Agency and the health care and academic sectors examined the question of whether mercury-containing amalgam used in clinical dentistry produced adverse health effects. This review was coordinated by the Committee to Coordinate Environmental Health and related Programs of the PHS. The final CCEHRP report, issued in January, 1993, concluded the following with respect to human health and amalgam use:

> "At present, there is scant evidence that the health of the vast majority of people with amalgam is compromised, nor that removing amalgam fillings has a beneficial effect on health.

* * *

> There is no solid evidence of any harm for millions of Americans who have amalgam fillings.
>
> * * *
>
> There is no persuasive reason to believe that avoiding amalgams or having them removed will have a beneficial effect on health.
>
> [Cite: Public Health Service, U.S. Department of Health & Human Services, January 21, 1993.]

In March 1991, manufacturers stated to this Panel,

> "Periodically, concerns have surfaced that amalgam fillings may present a health hazard since they contain mercury as a component. Yet, no adverse health effects of mercury from dental amalgams have been scientifically demonstrated.
>
> "This Panel should be mindful that the issues before the Panel about use of mercury in dental amalgam fillings are only hypothetical questions. Although it may be reasonable and appropriate for the Food and Drug Administration ("FDA") and this Panel to revisit the scientific issues raised by medical devices previously classified, it would be premature and inappropriate to make any regulatory recommendations or decisions based upon the current questions raised. There is no valid scientific evidence to support any decision that would send the signal that dental amalgams are unsafe and affect more than 100 million people. Such a message would needlessly raise public anxiety and have devastating adverse public health consequences."

This remains true today. In 1991, Dr. Benson described the difficult environment in which these scientific discussions must take place:

> "We must recognize that we are attempting to address the issue of amalgam safety in an emotionally charged atmosphere in which strong opinions abound."

This also remains as true today as it was then. Nonetheless, the research has advanced, and continues to do so, and our Committee is proud of its role.

We appreciate the opportunity to give you this update report on ADTA's viewpoint on dental amalgam, and on what has transpired since the March, 1991 Panel meeting where this issue was discussed. Although studies have shown that a minute amount of mercury is released from dental amalgams during chewing, toothbrushing and other activities that abrade the restoration,

there is no credible scientific evidence linking mercury in dental amalgams to any adverse human health effects, other than rare allergic reactions. We look forward to the completion of the current NIDR study. As outlined above, careful and thorough consideration by NIDR, CCEHRP and international health authorities confirm the conclusion reached by the Panel in 1991 that there is no data showing a direct hazard to human health from dental amalgams.

Ex. 10

Issued in Kansas City, Missouri, on April 14, 1998.

Michael Gallagher,

Manager, Small Airplane Directorate, Aircraft Certification Service.

[FR Doc. 98-10596 Filed 4-21-98; 8:45 am]

BILLING CODE 4910-13-U

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket Nos. 75N-183F, 75N-183D, and 80N-0280]

RIN 0910-AA01

Status of Certain Additional Over-the-Counter Drug Category II and III Active Ingredients

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule stating that certain ingredients in over-the-counter (OTC) drug products are not generally recognized as safe and effective or are misbranded. FDA is issuing this final rule after considering the reports and recommendations of various OTC drug advisory review panels and public comments on proposed agency regulations, which were issued in the form of a tentative final monograph (proposed rule). Based on the absence of substantive comments in opposition to the agency's proposed nonmonograph status for these ingredients, as well as the failure of interested parties to submit new data or information to FDA under the regulation, the agency has determined that the presence of these ingredients in an OTC drug product would result in that drug product not being generally recognized as safe and effective or would result in misbranding. This final rule is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Effective October 19, 1998.

FOR FURTHER INFORMATION CONTACT: Gerald M. Rachanow, Center for Drug Evaluation and Research (HFD-560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-2307.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of November 7, 1990 (55 FR 46914), FDA published under § 330.10(a)(7)(ii) (21 CFR 330.10(a)(7)(ii)), a final rule on the status of certain OTC drug Category II and III active ingredients. That final rule declared as not generally recognized as safe and effective certain active ingredients that had been proposed as nonmonograph (Category II or Category III) under the agency's OTC drug review. The periods for submission of comments and new data following the publication of a notice of proposed rulemaking (NPRM) had closed and no significant comments or new data had been submitted to upgrade the status of these ingredients. In each instance, a final rule for the class of ingredients involved had not been published to date.

In the **Federal Register** of May 10, 1993 (58 FR 27636), FDA published a final rule establishing that certain additional active ingredients in OTC drug products are not generally recognized as safe and effective or are misbranded. That final rule included active ingredients from a number of OTC drug rulemakings that were not covered by the November 7, 1990, final rule. (See Table I (58 FR 27636 at 27639 to 27641) for a list of OTC drug rulemakings and active ingredients covered by that final rule.)

At that time, there were other OTC drug review rulemakings for which the period for submission of comments and/or new data was still pending. Those periods have now closed, and there are a number of active ingredients for which no significant comments or new data were submitted. In each instance, a final rule for the class of ingredients involved has not been published to date. This final rule addresses some of the Category II and Category III active ingredients in those classes of ingredients, specifically active ingredients considered in the rulemakings for OTC vaginal contraceptive, first aid antiseptic, and antimicrobial diaper rash drug products.

In the advance notice of proposed rulemaking (ANPRM) for OTC vaginal contraceptive drug products (45 FR 82014, December 12, 1980), the Advisory Review Panel on OTC Contraceptives and Other Vaginal Drug Products placed phenylmercuric acetate and phenylmercuric nitrate in Category II for safety and placed dodecaethylene glycol monolaurate (polyethylene glycol 600 monolaurate), laureth 10S, and methoxypolyoxyethyleneglycol 550 laurate in Category III for efficacy. In the tentative final monograph (TFM) for OTC vaginal contraceptive drug products (60 FR 6892, February 3, 1995), the agency proposed that all of these ingredients be nonmonograph. In response to this TFM (NPRM), the agency received no comments or data relating to the safety and effectiveness of these ingredients.

In the ANPRM for mercury containing drug products for OTC topical antimicrobial use (47 FR 436, January 5, 1982), the Advisory Review Panel on OTC Miscellaneous External Drug Products placed all mercury compounds in Category II for topical antimicrobial use. This included the following ingredients: Ammoniated mercury; calomel (mercurous chloride); merbromin (mercurochrome); mercuric chloride (bichloride of mercury, mercury chloride); mercufenol chloride (ortho-chloromercuriphenol, ortho-hydroxyphenylmercuric chloride); mercuric salicylate; mercuric sulfide (red mercuric sulfide); mercuric oxide, yellow; mercury; mercury chloride; mercury oleate; nitromersol; para-chloromercuriphenol; phenylmercuric nitrate; thimerosal; vitromersol; and zyloxin. In the NPRM for OTC first aid antiseptic drug products (56 FR 33644, July 22, 1991), the agency proposed that all of these ingredients were either Category II or Category III. In response to this NPRM, the agency received no comments or data relating to the safety and effectiveness of these ingredients.

In an amendment to the proposed rulemaking for OTC topical antimicrobial drug products (55 FR 25246, June 20, 1990), the agency proposed that p-chloromercuriphenol and all other ingredients containing mercury were Category II for the treatment and prevention of diaper rash. In response to this NPRM, the agency received no comments or data relating to the safety and effectiveness of these ingredients.

II. Affected Rulemakings and Category II and III Ingredients

Table I of this document lists the titles and docket numbers of the specific rulemakings containing active ingredients that are addressed in this document, together with the publication dates of the ANPRM and the NPRM, as well as the closing dates for comments and submission of new data for each rulemaking. FDA advises that the active ingredients discussed in this document (see Table II of section II of this document) will not be included in the relevant final monographs because they have not been shown to be generally recognized as safe and effective for their intended use. The agency further advises that these ingredients should be eliminated from OTC drug products 6 months after the date of publication in the **Federal Register** of this final rule regardless of whether further testing is undertaken to justify future use.

The agency points out that publication of a final rule does not preclude a manufacturer's testing an ingredient. New, relevant data can be submitted to the agency at a later date as the subject of a new drug application that may provide for prescription or OTC marketing status. (See part 314 (21 CFR part 314).) As an alternative, where there are adequate data establishing general recognition of safety and effectiveness, such data may be submitted in an appropriate citizen petition to amend or establish a monograph, as appropriate. (See § 10.30 (21 CFR 10.30).)

TABLE I.—OTC DRUG RULEMAKINGS COVERED BY THIS FINAL RULE

Rulemaking and action	Publication date	Comment closing date	New data closing date
(1) *Vaginal contraceptive drug products*			
(Docket No. 80N–0280)			
Advance notice of proposed rulemaking (ANPRM)	December 12, 1980	March 12, 1981	Not applicable (N/A)
Notice of proposed rulemaking (NPRM)	February 3, 1995	June 5, 1995	February 5, 1996
(2) *First aid antiseptic drug products*			
(Docket No. 75N–0183)			
ANPRM	January 5, 1982	April 5, 1982	N/A
(Docket No. 75N–183F)			
NPRM	July 22, 1991	January 2, 1992	July 22, 1992
(3) *Antimicrobial diaper rash drug products*			
(Docket No. 75N–0183)			
ANPRM	September 7, 1982	December 6, 1982	January 5, 1983
(Docket No. 75N–183D)			
NPRM	June 20, 1990	December 17, 1990	June 20, 1991

Based on the criteria discussed above, FDA concludes that the following ingredients are not generally recognized as safe and effective and are misbranded when labeled as OTC drugs for the following uses:

TABLE II.—INGREDIENTS COVERED BY THIS FINAL RULE

Rulemaking and ingredients	Ingredient classification	
	Advance notice of proposed rulemaking	Notice of proposed rulemaking
(1) *First aid antiseptic drug products:*		
(Docket No. 75N–183F)		
Ammoniated mercury	II	II
Calomel (mercurous chloride)	II	III
Merbromin (mercurochrome)	II	III
Mercufenol chloride (ortho-chloromercuriphenol, ortho-hydroxyphenylmercuric chloride)	II	III
Mercuric chloride (bichloride of mercury, mercury chloride)	II	II
Mercuric oxide, yellow	II	II
Mercuric salicylate	II	II
Mercuric sulfide, red	II	II
Mercury	II	II
Mercury oleate	II	II
Mercury sulfide	II	II
Nitromersol	II	II
Para-chloromercuriphenol	II	II
Phenylmercuric nitrate	II	III
Thimerosal	II	II
Vitromersol	II	II
Zyloxin	II	II
(2) *Vaginal contraceptive drug products:*		
(Docket No. 80N–0280)		
Dodecaethylene glycol monolaurate) (polyethylene glycol 600 monolaurate)	III	III
Laureth 10S	III	III
Methoxypolyoxyethyleneglycol 550 laurate	III	III
Phenylmercuric acetate	II	II
Phenylmercuric nitrate	II	II
(3) *Antimicrobial diaper rash drug products:*		
(Docket No. 75N–183D)		
Para-chloromercuriphenol	NA	II
Any other ingredient containing mercury	NA	II

III. The Agency's Final Conclusions on Certain OTC Drug Category II and III Ingredients

No substantive comments or additional data have been submitted to the OTC drug review to support any of the ingredients listed in Table II of this document as being generally recognized as safe and effective for the specified OTC uses. The agency has determined that these ingredients should be deemed not generally recognized as safe and effective for OTC use before a final monograph for each respective drug category is established. Accordingly, any drug product containing any of these ingredients and labeled for the OTC use identified in Table II of this document will be considered nonmonograph and misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352) and a new drug under section 201(p) of the act (21 U.S.C. 321(p)) for which an approved application under section 505 of the act (21 U.S.C. 355) and part 314 of the regulations is required for marketing. As an alternative, where there are adequate data establishing general recognition of safety and effectiveness, such data may be submitted in a citizen petition to amend the appropriate monograph to include any of the above ingredients in OTC drug products in Table II of this document. (See § 10.30.) Any OTC drug product containing any of the ingredients in Table II of this document and labeled for the use identified in Table II of this document initially introduced or initially delivered for introduction into interstate commerce after the effective date of this final rule that is not the subject of an approved application will be in violation of sections 502 and 505 of the act and, therefore, subject to regulatory action. Further, any OTC drug product subject to this final rule that is repackaged or relabeled after the effective date of the rule would be required to be in compliance with the rule regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the rule at the earliest possible date.

IV. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant impact on a substantial number of small entities, an agency must analyze significant regulatory options that would minimize any significant impact of the rule on small entities.

Title II of the Unfunded Mandates Reform Act (2 U.S.C. 1501 *et seq.*) requires that agencies prepare a written statement and economic analysis before proposing any rule that may result in an expenditure in any 1 year by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million (adjusted annually for inflation).

The agency believes that this final rule is consistent with the principles set out in the Executive Order and in these two statutes. The purpose of this final rule is to act on the proposed nonmonograph status of certain ingredients in advance of finalization of other monograph conditions in order to expedite completion of the OTC drug review. There are a limited number of products currently marketed that will be affected by this rule. Of the 17 mercury active ingredients included in the final rule, the agency is aware of 12 OTC drug products containing merbromin, 1 product containing phenylmercuric nitrate, and 7 products containing thimerosal. These products are marketed by eight different manufacturers, most of which are considered small entities, using the U.S. Small Business Administration designation for this industry (750 employees). The agency is not aware of any topical antimicrobial diaper rash or vaginal contraceptive drug products containing any of the active ingredients included in this final rule.

Manufacturers of these products will no longer be able to market products containing the ingredients included in this final rule after its effective date. While the manufacturers will incur a loss of revenue for these products, the agency believes the economic impact will be minimal for several reasons. A. C. Nielsen (Nielsen), a recognized provider of market research business information and analysis, maintains product data from a sample of 4,000 retail outlets selected to represent the geographical and retail characteristics of the U.S. OTC market. Based on these Nielsen data, the agency estimates that total sales for these products represent less than 0.1 percent of all sales of OTC first aid drug products. For the affected companies, these product sales comprised less than 1 percent of OTC drug revenues. The industry has been aware of the status of these products since 1982, and all of the manufacturers identified by FDA also produce products containing ingredients proposed for inclusion in the monograph. The lost sales from the nonmonograph products are expected to be offset by increased sales of the substitute products.

The agency considered, but rejected, not acting on these ingredients in advance of the finalization of other monograph conditions. The final monographs for OTC topical antimicrobial and vaginal contraceptive drug products are not expected to be completed for a period of time. The agency also considered publishing an additional notice specifying that the determinations on the ingredients in this final rule would be included in a final rule prior to publication of a final rule including the determinations on ingredients for which new data and information have been submitted. However, safety and effectiveness have not been established for the ingredients included in this current final rule and manufacturers have not submitted the necessary data in response to earlier opportunities. The agency's experience has been that under these circumstances companies have not submitted data in response to yet another opportunity. Consumers will benefit from the early removal from the marketplace of products containing ingredients for which safety and effectiveness have not been established. Consumers can then purchase products containing only ingredients proposed for monograph status. Manufacturers who choose to reformulate or replace affected products will be able to use alternative ingredients that are proposed as monograph conditions without incurring any additional expense of clinical testing for those ingredients. As noted previously, FDA believes that most manufacturers currently produce such products.

While this final rule may cause manufacturers to discontinue marketing or to reformulate some products prior to issuance of the applicable final monograph, these manufacturers have known for some time that if adequate data were not submitted to support safety and effectiveness, cessation of marketing of the current products would be required, in any event, when the final monographs are published. Because this rule imposes no additional reporting or recordkeeping requirements, no additional professional skills are necessary to comply.

The analysis shows that this final rule is not economically significant under Executive Order 12866 and that the agency has considered the burden to small entities. Based on the above analysis, the agency does not believe that the majority of manufacturers will incur a significant economic impact. However, there may be a few that could incur significant reformulation costs or inventory losses. Thus, this economic analysis, together with other relevant sections of this document, serves as the agency's final regulatory flexibility analysis, as required under the Regulatory Flexibility Act. Finally, this analysis shows that the Unfunded Mandates Reform Act does not apply to the final rule because it would not result in an expenditure in any 1 year by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million.

V. Environmental Impact

The agency has determined under 21 CFR 25.31(c) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects in 21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 310 is amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b-360f, 360j, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b-263n.

2. Section 310.545 is amended by adding paragraphs (a)(27) and (a)(28), by revising paragraph (d) introductory text, by reserving paragraphs (d)(26) and (d)(27), and by adding paragraph (d)(28) to read as follows:

§ 310.545 Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.

(a) * * *

(27) *Topical antimicrobial drug products*—(i) *First aid antiseptic drug products.*

Ammoniated mercury
Calomel (mercurous chloride)
Merbromin (mercurochrome)
Mercufenol chloride (ortho-chloromercuriphenol, ortho-hydroxyphenylmercuric chloride)
Mercuric chloride (bichloride of mercury, mercury chloride)
Mercuric oxide, yellow
Mercuric salicylate
Mercuric sulfide, red
Mercury
Mercury oleate
Mercury sulfide
Nitromersol
Para-chloromercuriphenol
Phenylmercuric nitrate
Thimerosal
Vitromersol
Zyloxin

(ii) *Diaper rash drug products.*

Para-chloromercuriphenol
Any other ingredient containing mercury

(28) *Vaginal contraceptive drug products.*

Dodecaethylene glycol monolaurate (polyethylene glycol 600 monolaurate)
Laureth 10S
Methoxypolyoxyethyleneglycol 550 laurate
Phenylmercuric acetate
Phenylmercuric nitrate
Any other ingredient containing mercury

* * * * *

(d) Any OTC drug product that is not in compliance with this section is subject to regulatory action if initially introduced or initially delivered for introduction to interstate commerce after the dates specified in paragraphs (d)(1) through (d)(28) of this section.

* * * * *

(28) October 22, 1998, for products subject to paragraphs (a)(27) and (a)(28) of this section.

Dated: April 8, 1998.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 98-10578 Filed 4-21-98; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF THE INTERIOR

Office of Surface Mining Reclamation and Enforcement

30 CFR Part 938

[PA-112-FOR]

Pennsylvania Regulatory Program

AGENCY: Office of Surface Mining Reclamation and Enforcement (OSM), Interior.

ACTION: Final rule; approval of amendments.

SUMMARY: OSM is approving, with certain exceptions, a proposed amendment to the Pennsylvania permanent regulatory program (hereinafter referred to as the Pennsylvania program) under the Surface Mining Control and Reclamation Act of 1977 (SMCRA). The amendment revises the Pennsylvania program to incorporate changes made by Pennsylvania House Bill 1075 and subsequent Pennsylvania law Act 1994-114. The amendment is intended to provide special authorization for coal refuse disposal in areas previously affected by mining which contain pollutional discharges.

EFFECTIVE DATE: April 22, 1998.

FOR FURTHER INFORMATION CONTACT: Robert J. Biggi, Director, Office of Surface Mining Reclamation and Enforcement, Harrisburg Field Office, Harrisburg Transportation Center, Third Floor, Suite 3C, 4th and Market Streets, Harrisburg, Pennsylvania 17101. Telephone: (717) 782-4036.

SUPPLEMENTARY INFORMATION:

I. Background on the Pennsylvania Program

On July 31, 1982, the Secretary of the Interior conditionally approved the Pennsylvania program. Background information on the Pennsylvania program including the Secretary's findings, the disposition of comments, and a detailed explanation of the conditions of approval of the Pennsylvania program can be found in the July 30, 1982, **Federal Register** (47 FR 33050). Subsequent actions concerning the conditions of approval and program amendments are identified at 30 CFR 938.11, 938.12, 938.15 and 938.16.

II. Submission of the Amendment

By letter dated September 14, 1995 (Administrative Record Number PA 837.01), Pennsylvania submitted an amendment to the Pennsylvania program. The amending language is contained in Pennsylvania House Bill 1075 and was enacted into Pennsylvania law as Act 1994-124. The amendments change Pennsylvania's Coal Refuse Disposal Act (of September 24, 1968 (P.L. 1040, No. 318) and amended on October 10, 1980 (P.L. 807, No. 154)) to provide for authorization for refuse disposal in areas previously affected by mining which contain pollutional

Ex. 11

Subj: **Fwd: Dental amalgam question**
Date: 1/5/04 12:55:30 PM Eastern Standard Time
From: NoHGpam
To: AYokoyama
CC: Hgsz

This is the answer I received from Susan Runner. I will follow up later today. In the meantime if you have any comments onthis - please respond to me.

Pam Floener

Forwarded Message:
Subj: **Fwd: Dental amalgam question**
Date: 1/5/04 12:42:32 PM Eastern Standard Time
From: Rmacnc
To: NoHGpam

Forwarded Message:
Subj: **RE: Dental amalgam question**
Date: 1/5/04 11:41:38 AM Eastern Standard Time
From: MSR@CDRH.FDA.GOV
To: Rmacnc@aol.com
Sent from the Internet (Details)

In answer to your question about how dental amalgams are regulated.
The medical device amendments of 1976 classified most known medical devices into class I, II or III. At that time dental mercury and amalgam alloy were classified. The mercury was classified into class I and the alloy into class II. The combined form of the device that is most commonly seen in dental offices known as the encapsulated dental amalgam was not classified as a separate device. The definition of the alloy in the Code of Federal Regulations states that the device consists of a metallic substance intended to be mixed with mercury to forma filling material. We also have a regulation for the Dental Amalgam Capsule which is the container for the mixture of the alloy and the mercury to form dental amalgam. Although the encapsulated form was not specifically mentioned in the original classification it is considered a combination of two classified devices, the alloy and the mercury. As with all combination devices it is regulated in the class that is the highest (the alloy, class II).
For your question about regulated vs. approved. Regulations indicate which medical products are under the purview of FDA. In other words which products require a marketing application before a manufacturer is allowed to sell to the public. Approval and clearance are the words that are used to indicate the FDA's decision about a medical device. Class III devices are "approved" and class I and II devices are "cleared" by the agency. I hope this is helpful to you. If you have any further questions please feel free to call me at the number listed below.,

Susan Runner DDS,MA

Mr. BURTON. Thank you, Dr. Fischer. You've been doing yeoman's service in this area, and I really appreciate it.

Dr. Deth, you were supposed to also bring testimony from this recent study. Could you quickly go into that?

STATEMENT OF MADY HORNIG, M.D., PH.D., ASSISTANT PROFESSOR OF EPIDEMIOLOGY, COLUMBIA UNIVERSITY

Mr. DETH. Yes, thank you. I was asked by Dr. Mady Hornig to provide her summary, and I'll do that now.

Mr. BURTON. OK.

Mr. DETH. Chairman Burton, Congresswoman Watson and members of the subcommittee, thank you for the opportunity to submit for the record this statement regarding our new animal model of the toxicity of thimerosal and its implications for human health. I regret that I am unable to personally present this testimony due to a family medical emergency.

Our work addresses whether genes are important in determining if mercury exposures akin to those in childhood immunizations can disrupt brain development and function. I also submit for the record an electronic copy of the first paper published on this animal model in the Nature Publishing Group Journal Molecular Psychiatry.

The premise of our research is that if mercury in vaccines creates risks for neurodevelopmental disorders such as autism, genetic differences are likely to contribute to that risk. We built upon an extensive existing literature on toxicity of other forms of mercury in in-bred mouse strains that affirmed the importance of specific genes controlling immune responses in determining mercury-induced autoimmune outcomes in mice.

Earlier studies, however, did not use the form of mercury present in vaccines known as thimerosal, and did not consider whether intramuscular repetitive administration during early post-natal development, when the brain and immune systems are still maturing, might intensify toxicity. Based on reports of immune disturbances and family history of autoimmune disease in a subset of children with autism, we hypothesize that immune response genes linked to mercury immunotoxicity in mice would predict damage following low dose vaccine based mercury in our mouse model.

Our predictions were confirmed. Using thimerosal dosages and timing that approximated the childhood immunization schedule, our model of post-natal thimerosal neural toxicity demonstrated that the genes in mice that predict mercury-related immunotoxicity also predicted neurodevelopmental damage.

Features reminiscent of those observed in autism occurred in the mice of the genetically sensitive strain, including generalized behavioral impoverishment and abnormal reaction to novel environments, enlargement of the hippocampus, a region of the brain involved in learning and memory, correlation of hippocampal enlargement with abnormalities in exploration and anxiety, increased packing density of neurons in hippocampus and disturbances in glutamate receptors and transporters.

Only mice carrying the H2 susceptibility gene showed these autism-like effects. Two mouse strains with different H2 genes did

not demonstrate adverse consequences following thimerosal exposure.

It's important to empathize that these animal model studies do not provide conclusive evidence regarding a link between mercury exposure and human autism. Nonetheless, the finding that a specific genetic constraint profoundly alters the brains and behavior of thimerosal-exposed mice confirms the biological plausibility of thimerosal neurotoxicity, provides critical guidance for the interpretation of existing epidemiologic investigations into the potential association of thimerosal with neurodevelopmental disorders, and suggests important new avenues for future research.

Our work implies that if genetic factors are operative in mediating a link between thimerosal and autism in humans, then studies that fail to consider genetic susceptibility factors will be compromised in their ability to detect a statistical significant effect, even if one exists.

Recent findings presented at scientific meetings but as yet unpublished suggest that thimerosal neurotoxicity in susceptible mice involves the generation of auto-antibodies targeting brain components. This autoimmune response persists long after the presence of mercury can no longer be detected.

If confirmed, these findings will enable us to develop a human diagnostic test to determine whether some individuals with autism have similar autoantibodies present in their peripheral blood. Such work would not only bring us a step closer to identifying the genes associated with thimerosal neurotoxicity in humans, facilitating prevention programs, it would also validate the utility of this animal model for the development of safe and effective modes of intervention.

It is highly likely that the neurotoxic effects of cumulative mercury burden, including exposure to other sources or forms of mercury, follow similar patterns of genetic restriction. It's also likely that similar genetic factors influence the neurotoxicity observed following exposure to xenobiotics other than mercury. Age, developmental status and the time of exposure, nutritional factors and gender are known to influence outcomes.

We have limited ability to explain the interplay of such factors in humans. Consider the example of the disparate cognitive outcomes reported in children in the Faroe Islands and the Seychelles after similar prenatal methylmercury exposures. The reasons for this divergence remain unclear. The design of future epidemiologic studies must take into account the possibility of multiple xenobiotic exposures as well as the influence of factors that modulate risk. Our studies have important implications for understanding the role of gene-environment interactions in the pathogenesis of autism and related neurodevelopmental disorders.

I refer subcommittee members to our recent publication in Molecular Psychiatry where experimental findings and their implications are discussed in more detail. Thank you for your attention, Mady Hornig, New York, NY.

[The prepared statement of Dr. Hornig follows:]

CONGRESSIONAL TESTIMONY

U.S. HOUSE OF REPRESENTATIVES
THE SUBCOMMITTEE ON HUMAN RIGHTS AND WELLNESS
COMMITTEE ON GOVERNMENT REFORM

SEPTEMBER 8, 2004 HEARING

TRUTH REVEALED:
NEW SCIENTIFIC DISCOVERIES
REGARDING MERCURY
IN MEDICINE AND AUTISM

submitted by:

Mady Hornig, MD
Director of Translational Research
Jerome L. and Dawn Greene Infectious Disease Laboratory

and

Associate Professor of Epidemiology
Mailman School of Public Health
Columbia University

Chairman Burton, Congressman Watson, and Members of the Subcommittee, Thank you for the opportunity to submit for the record this statement regarding our new animal model of the toxicity of thimerosal (ethylmercury preservative in vaccines) and its implications for human health. I regret that I am unable to personally present this testimony today due to a family medical emergency. Our work addresses whether genes are important in determining if mercury exposures akin to those in childhood immunizations can disrupt brain development and function. I also submit for the record an electronic copy of the first paper published on this animal model in the Nature Publishing Group journal, *Molecular Psychiatry* (Hornig M, Chian D, Lipkin WI. Neurotoxic effects of postnatal thimerosal are mouse strain dependent. *Mol Psychiatry* 2004;*9*:833-845).

The premise of our research is that if mercury in vaccines creates risk for neurodevelopmental disorders such as autism, genetic differences are likely to contribute to that risk. We built upon an extensive, existing literature on toxicity of other forms of mercury in inbred mouse strains that affirmed the importance of specific genes controlling immune responses (major histocompatibility complex, or MHC) in determining mercury-induced autoimmune outcomes in mice. Earlier studies, however, did not use the form of mercury present in vaccines, known as thimerosal, and did not consider whether intramuscular, repetitive administration

during early postnatal development, when the brain and immune systems are still maturing, might intensify toxicity. Based on reports of immune disturbances and family history of autoimmune disease in a subset of children with autism, we hypothesized that immune response genes linked to mercury immunotoxicity in mice would predict damage following low-dose, vaccine-based mercury in our mouse model.

Our predictions were confirmed. Using thimerosal dosages and timing that approximated the childhood immunization schedule, our model of postnatal thimerosal neurotoxicity demonstrated that the genes in mice that predict mercury-related immunotoxicity also predicted neurodevelopmental damage. Features reminiscent of those observed in autism occurred in the mice of the genetically sensitive strain, including: generalized behavioral impoverishment and abnormal reaction to novel environments; enlargement of the hippocampus, a region of the brain involved in learning and memory; correlation of hippocampal enlargement with abnormalities in exploration and anxiety; increased packing density of neurons in hippocampus; and disturbances in glutamate receptors and transporters. Only mice carrying the $H\text{-}2^{s}$ susceptibility gene showed these autism-like effects (SJL/J mice). Two mouse strains with different H-2 genes (C57BL6/J mice, $H\text{-}2^{b}$; BALB/cJ mice, $H\text{-}2^{d}$) did not demonstrate adverse consequences following thimerosal exposure.

It is important to emphasize that these animal model studies do not provide conclusive evidence regarding a link between mercury exposure and human autism. Nonetheless, the finding that a specific genetic constraint profoundly alters the brains and behavior of thimerosal-exposed mice confirms the biological plausibility of thimerosal neurotoxicity, provides critical guidance for the interpretation of existing epidemiologic investigations into the potential association of thimerosal with neurodevelopmental disorders, and suggests important new avenues for future research. Our work implies that if genetic factors are operative in mediating a link between thimerosal and autism in humans, then studies that fail to consider genetic susceptibility factors will be compromised in their ability to detect a statistically significant effect even if one exists.

Recent findings, presented at scientific meetings but as yet unpublished, suggest that thimerosal neurotoxicity in susceptible mice involves the generation of autoantibodies targeting brain components. This autoimmune response persists long after the presence of mercury can no longer be detected. If confirmed, these findings will enable us to develop a human diagnostic test to determine whether some individuals with autism have similar autoantibodies present in their peripheral blood. Such work would not only bring us a step closer to identifying the genes associated with thimerosal neurotoxicity in humans, facilitating prevention programs, it would also validate the utility of this animal model for the development of safe and effective modes of intervention.

It is highly likely that the neurotoxic effects of cumulative mercury burden, including exposure to other sources or forms of mercury (thimerosal in products other than vaccines; methylmercury in contaminated fish), follow similar patterns of genetic restriction; it is also likely that similar genetic factors influence the neurotoxicity observed following exposure to xenobiotics other than mercury (e.g., PCBs, the PBDEs used as flame retardants in computers, and infectious agents). Age and developmental status at the time of exposure, nutritional factors, and gender are also known to influence outcomes. We have limited ability to explain the interplay of such factors in humans; consider the example of the disparate cognitive outcomes reported in children in the Faroe Islands and the Seychelles after similar prenatal methylmercury exposures. The reasons for this divergence remain unclear. The design of future epidemiologic studies must take into account the possibility of multiple xenobiotic exposures as well as the influence of factors that modulate risk. Our studies have important implications for understanding the role of gene-environment interactions in the pathogenesis of autism and related neurodevelopmental disorders.

I refer Subcommittee Members to our recent publication in *Molecular Psychiatry* where experimental findings and their implications are discussed in more detail.

Thank you for your attention.
Mady Hornig, MD
New York, NY

Mr. BURTON. Thank you, Dr. Deth. And thank her for her research. We really appreciate that.

Mr. DETH. Thank you.

Mr. BURTON. So what she's saying is, if there's a genetic possibility that the mercury in these mice can cause autistic like symptoms?

Mr. DETH. That's right. The theme of her work, which parallels the theme of part of what I mentioned as well, is that genetic factors that are probably exclusively or highly over-represented in autistic children are in fact giving them a higher vulnerability to thimerosal, as they were in her mouse model. And her mouse had certain genetic factors, autistic children no doubt have their own genetic factors that bring risk to their metal exposure.

Mr. BURTON. In the charts that you showed earlier, it showed two children from the same family. One had evidently genetic risk factors that the other one didn't, and as a result they suffered autism while the other one didn't. So that's, you think, pretty common among the population?

Mr. DETH. At this point, we've only analyzed about half a dozen such paired siblings, that is, siblings of the same sex that either did or didn't develop autism. So far we have found a correlation with thimerosal sensitivity, a higher thimerosal sensitivity and the occurrence of autism.

At the same time, in that same larger set that we hope to eventually get data on, a bigger data set, we can see the presence of these genetic risk factors as polymorphisms in the very same genes that affect this methylation process that thimerosal inhibits. So we are able now in a small number of families to show that genes do make a difference and where they do affect the outcome has to do with the methylation and thimerosal sensitive methylation pathways.

Mr. BURTON. You said B12 administered in a certain way does help cure or clean out the autistic problem in children?

Mr. DETH. A remarkable finding presented about a year and a half ago by Dr. James Neubrander at a meeting of Defeat Autism Now, or DAN meeting, was that when he administered methylB12 injections to children in his autism practice, that a significant number of them, that he estimated to be at least 75 percent, experienced significant improvement in their autism symptoms. In a followup presentation, he indicated that there was again a significant number of those who were so well benefited that the independent neurologists' evaluation concluded that they no longer had autism.

Now, this is not a large proportion that in fact were off the autism spectrum. But it is significant that even the numbers that he found were able to be so significantly improved that they could be thought to be autism-free. But they were still under treatment with methylB12.

Mr. BURTON. So some children can be helped, but it's not a cure-all?

Mr. DETH. That's easily said. It's unfortunate that it isn't even effective for a larger number of children. But it is effective for many.

Mr. BURTON. If thimerosal, or the mercury, is indeed the culprit for causing some of this autism, and from Dr. Just obviously, it's

not the only cause of autism, why do you think the IOM committee gave it a clean bill of health?

Mr. DETH. As has been reviewed here, the IOM report very clearly says that their conclusion was based simply on a subset of the epidemiologic studies that they valued at a higher level than other studies, as you pointed out earlier. The hypotheses or the scientific data, in fact, that they did not include in their consideration they branded as speculative.

I suppose it is speculative in that this information has not been out in the literature for more than a year or a year and a half. But in fact, it is not speculative, it's hard science. Their conclusions were simply based upon epidemiologic studies that they selected.

Mr. BURTON. They were very selective in their findings?

Mr. DETH. It appears to me personally that they had a mission to preserve vaccine reputation and that they were willing to turn a blind eye to the body of information indicating that thimerosal could have caused autism in a sub-population for the greater benefit.

Mr. BURTON. You're being very diplomatic.

Mr. DETH. I'm trying to be subjective on that matter.

Mr. BURTON. In other words, they would listen to the ones that were going to benefit certain people that they wanted to benefit, and they turned their eyes away from the five studies that showed that there was a correlation.

Dr. Just, you were talking about this under-connectivity in the brains of autistic individuals. Do you think, and this has nothing to do with the mercury in vaccines, but it is interesting, do you think that they will be able to correct that in people in the future?

Mr. JUST. Yes, in two ways. First of all, in the short run, I think we can design therapies, and test them of course, that might be more effective than current therapies. It's not going to be the cure-all. But I think there are ways to promote the kind of thinking to get those key players to work together in the face of and in spite of the under-connectivity.

As you say, I don't know the exact number of people who have autism now. They need to have the most effective treatment possible given them. I think that's one possible outcome of this kind of research.

But in the slightly longer run, can we hope to cure it? I think not next year but in the long run, I think we can. And I think the way to do it is through a science called converging methods. Many, many kinds of evidence that point to the same thing, that's how you can be most sure, I think.

Mr. BURTON. If you have somebody who has had their brain cells killed, in part, by mercury, could that be one of the reasons why you have this non-connectivity between the two portions?

Mr. JUST. There are definitely abnormalities in brain cells in people with autism.

Mr. BURTON. The causes we're not sure of.

Mr. JUST. That's right. But let me tell you one of the remarkable things about the brain. It has tremendous plasticity. People have a stroke and you can just visibly see an enormous number of brain cells being killed right then and there. And you see sometimes, not in everybody, sometimes you see a remarkable recovery.

Mr. BURTON. Regeneration.

Mr. JUST. I don't know about regeneration. Other parts of the brain taking over. I've seen this in my own research in stroke recovery, and I think you can promote some of this. So I think there is tremendous potential there for that kind of therapy.

Mr. BURTON. Ms. Redwood, we appreciate your being with us again. You provided the subcommittee a newly released report from SafeMinds, outlining the last 5 years of research. In your opinion, did the CDC take this possible thimerosal-autism connection seriously? Did they pay any attention to that? Did they look at it?

Ms. REDWOOD. Mr. Chairman, they did look at the issue. My concern is that what they saw was so disturbing to them, it was an unthinkable thought that a program that had been so successful that it could have possibly caused injury. I think it was an unthinkable thought for CDC. And when they saw this initial data, it was so disturbing to them that they purposefully went about devising methods for that data to no longer be significant.

There's a number of manipulations that they did to that data along the 3 years or 4 years that they had it that made those highly statistically significant dose dependent relationships between exposure to thimerosal and adverse neurodevelopmental outcomes slowly go away with each new generation. So I think in my personal opinion they didn't want to find the truth.

Mr. BURTON. Well, I think they're aware of the problem to a much greater degree than any of us would like to believe. When we passed the Homeland Security Bill, and I've brought this up at committee hearings before, at the 11th hour, this committee wrote most of the Homeland Security Bill, and at the 11th hour late at night, they put a provision in the bill which would protect pharmaceutical companies from lawsuits pending from a component part of a vaccination, i.e. thimerosal, which was a preservative. And that, had it been passed into law, would have protected them from any type of legal remedy from these people who have been damaged, like your son or my grandson.

And we were able to get that out in the Senate and it's not the law. So there is still a liability exposure there, and it's more of, if Congress and the people in the industry that are doing this research, and come up with a compromise that would protect them from large class action lawsuits which could put some of them out of business if this is ever proven beyond a reasonable doubt, and a solution that would help the people who have been damaged like your son and my grandson, by giving them restitution.

We passed what we called the Vaccine Injury Compensation Fund back in the 1980's, which was designed to help people who were damaged. That fund now has probably $3 billion in it. That may not be enough to be able to take care of all the children who have been damaged, or the people who have been damaged by vaccines.

But when, and I'm not saying if, but I believe when it's proven that the mercury in vaccines has been a major contributing factor to these damaged kids, then there's going to be a tremendous amount of liability exposure for these pharmaceutical companies and then they're going to be out there all by themselves. That's why I suggested to them that we try to beef up the Vaccine Injury

Compensation Fund and at the same time that we could protect them from class action lawsuits, as long as they took care of the people that were damaged.

And then finally, get the mercury out of everything. Get it out of all vaccinations so that future generations of kids aren't going to be damaged.

We're not there yet, but with the body of evidence that's being developed by you, Dr. Deth, and the doctor that did the mice study, the body of evidence is growing. It's going to be, in my opinion, conclusive enough in the not too distant future that they're going to be put in this position.

So I'd just like to say, and I'm sure there's nobody from the pharmaceutical industry here today, well, maybe there is, it's time for them to sit down with the Members of Congress and people who are working in this area, and try to work out a way to beef up the Vaccine Injury Compensation Fund, No. 1, No. 2, get mercury out of all vaccinations or anything that goes into the human body, and third, we would be willing then to protect them from these class action lawsuits.

And Dr. Fischer, you and I have been friends and worked on this for a long, long time. That would include, I believe, getting mercury out of anything that goes into the body, including amalgams. It seems to me unbelievable that when you can't take the refuse from a mercury filling and flush it down the drain because it's so toxic, and you don't want to get it into the groundwater supply, that you have to put it into a container to protect the people from the contamination, that they put it in our mouths and say that if the filling cracks or if the vapors from it, that they are not going to damage the human brain. It just doesn't make sense to me.

In any event, do any of you have any last comments you'd like to make before we call this hearing closed? What's that? Do we have that?

For the media and anybody else, we have a video that we got from a research group in Canada. I'd like to show that one last time, because this may be the last hearing we'll have this year on this subject. So could we play that? It shows what happens when a minute amount of mercury is put in close proximity to a brain cell. So if we could run that real quickly.

[Video presented.]

Mr. BURTON. I think that shows pretty clearly, and that was in 1999, that's been 5 years ago, and we showed that to the CDC and the FDA and HHS, and they have paid virtually no attention to it.

Dr. Fischer, I'll let you make a final comment then we'll adjourn.

Dr. FISCHER. Thank you. I wanted to make one brief comment about that video. That's a study that our Academy helped fund. Dr. Fritz Larshager, the lead investigator on that, told us actually at a hearing here about a year ago when he testified before this committee that the amount of mercury that was used in that experiment was 1 million times less than the amount of mercury that is entranced the body on a daily basis from dental fillings. One million times less.

Mr. BURTON. Anybody else have any final comments you'd like to make? Yes, Dr. Deth.

Mr. DETH. In relation to Dr. Just's presentation, even though it didn't include thimerosal, I would like to just point out that the synchronization of brain waves seems to be a process that this methylation pathway involving dopamine receptors is also involved in. So it's interesting to me, and I didn't actually know Dr. Just before this morning, that you would see impairment of the synchronized brain activity that fits very well with impairment of methylation.

The other aspect that also makes his work link to ours is the fact that the synthesis of myelin, the white matter that was lower in autism in his study, and the corpus callosum is also dependent upon methylation. So an insult to that system could account for reduced white matter, as well as reduced synchronization of brain activity that would contribute to autism.

Mr. BURTON. Thank you, Dr. Deth. Dr. Just.

Mr. JUST. I'd like to take the opportunity to express our tremendous appreciation of the individuals with autism and their families who have participated in our studies and others. This is just a critical contribution to understanding autism, treating it effectively, finding a cure. We want to encourage others to do so. The pace of progress is only as fast as the number of individuals who volunteer increases. That can't be over-emphasized.

Mr. BURTON. Well, we would encourage anybody who has an autistic child or who has autism in their family to participate in those kinds of studies. They're not dangerous, there's no danger involved, but it is going to be helpful long term.

Ms. Redwood, do you have any last comments?

Ms. REDWOOD. Yes, and again I apologize for going over my presentation. It's just impossible——

Mr. BURTON. That's all right. We understand your enthusiasm.

Ms. REDWOOD [continuing]. To sum up 5 years in 5 minutes. But one of the things that concerns us at SafeMinds is the creation of the Brighton Collaboration. We would ask for your help in contacting CDC to look into this further.

Mr. BURTON. We will. In fact, the reports that we have, all this is going to be sent over to the CDC along with a number of questions, and to FDA. And we're going to ask them to respond. I'm not optimistic we're going to get any big change in their attitudes, but as the scientific research continues, I think it's going to become very evident that mercury is a major contributing factor to these neurological disorders, including autism.

Like I said before, I just don't understand the pharmaceutical industry, when we've already reached out to them to try to find a solution to this problem, getting mercury out of all vaccines, getting it out of amalgams, creating a fund, increasing the fund so we can take care of these people who have been damaged, and then finally, if they do that, protecting them from class action lawsuits, I just don't understand the down side to any of that. Nevertheless, we're not getting much response from them.

But we will continue working on this, and I thank you all for your diligence and your hard work. We stand adjourned.

[Whereupon, at 1:10 p.m., the subcommittee was adjourned.]

[The prepared statement of Hon. Elijah E. Cummings and additional information submitted for the hearing record follow:]

Statement of Congressman Elijah E. Cummings
House Government Reform
Subcommittee on Human Rights and Wellness Hearing
On
"Truth Revealed: New Scientific Discoveries Regarding Mercury in Medicine and Autism"
September 8, 2004 at 10:00 a.m.

Thank you, Mr. Chairman.

I want to thank you for holding this hearing to discuss new scientific findings about the effects mercury has on the body. I look forward to learning more about any alleged relationship between mercury in pediatric vaccines and dental amalgam to autism.

Although extensive research on autism continues to occur at federal agencies, such as the Centers for Disease Control and Prevention, the National Institutes of Health, and educational institutions such as the Center for Development and Behavior Learning at the University of Maryland School of Medicine in Baltimore, the causes of autism remain unknown. However, the growing awareness of autism, especially through this Committee, is leading to different scientific delving into the possible causes of this developmental disorder.

In fact, recent concerns have centered around the use of dental amalgam, otherwise known as "silver fillings," which are made up of about 50% mercury. Although dental amalgams have been widely used for over 150 years, improved dental health over the last few decades has led to the use of alternative materials. The concern is that dental amalgams give off a mercury vapor that could possibly be absorbed by a patient. The Center for Disease Control (CDC) has not ruled out that this absorption may be harmful, since there are insufficient human studies to determine otherwise. The National Institutes of Health (NIH) is currently conducting such a study and the results, which will prove critical to the dental amalgam safety debate, should be available in 2005.

The number of documented children suffering from autism is 1 out of every 166 and the rates of autism diagnosis are continually rising in every state. As such, it is important that research and awareness continue in the medical and educational community. Hearings such as this help to raise awareness, while shedding light on the different theories related to the causes of autism.

The witnesses here before us today are experts, and I look forward to hearing from them as they discuss the effects that mercury has on the body, and its possible link to autism.

Thank you, Mr. Chairman, for holding this hearing.

I yield back the balance of my time.

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Thimerosal Exposure in Infants and Developmental Disorders: A Prospective Cohort Study in the United Kingdom Does Not Support a Causal Association

Jon Heron, PhD; and Jean Golding, DSc; and the ALSPAC Study Team

ABSTRACT. *Objective.* **There is an established link between exposure to mercury and impaired childhood cognitive development and early motor skills. Thimerosal (also known as thiomersal), a preservative used in a number of children's vaccines, contains ethylmercury (an organic compound of mercury), and there has been concern that this exposure to mercury may be of some detriment to young children. The aim of this research was to test in a large United Kingdom population–based cohort whether there is any evidence to justify such concerns.**

Methods. **We used population data from a longitudinal study on childhood health and development. The study has been monitoring >14 000 children who are from the geographic area formerly known as Avon, United Kingdom, and were delivered in 1991–1992. The age at which doses of thimerosal-containing vaccines were administered was recorded, and measures of mercury exposure by 3, 4, and 6 months of age were calculated and compared with a number of measures of childhood cognitive and behavioral development covering the period from 6 to 91 months of age.**

Results. **Contrary to expectation, it was common for the unadjusted results to suggest a beneficial effect of thimerosal exposure. For example, exposure at 3 months was inversely associated with hyperactivity and conduct problems at 47 months; motor development at 6 months and at 30 months; difficulties with sounds at 81 months; and speech therapy, special needs, and "statementing" at 91 months. After adjustment for birth weight, gestation, gender, maternal education, parity, housing tenure, maternal smoking, breastfeeding, and ethnic origins, we found 1 result of 69 to be in the direction hypothesized—poor prosocial behavior at 47 months was associated with exposure by 3 months of age (odds ratio: 1.12; 95% confidence interval: 1.01-1.23) compared with 8 results that still supported a beneficial effect.**

Conclusions. **We could find no convincing evidence that early exposure to thimerosal had any deleterious effect on neurologic or psychological outcome.** *Pediatrics* **2004;114:577–583;** ***ALSPAC, cohort study, neurodevelopment, safety, thimerosal, thiomersal, mercury, vaccines.***

ABBREVIATIONS. wDTP, whole-cell diphtheria/tetanus/pertussis; DT, diphtheria/tetanus; ALSPAC, Avon Longitudinal Study of Parents and Children; DTP, diphtheria/tetanus/pertussis; SDQ, Strengths and Difficulties Questionnaire; OR, odds ratio; CI, confidence interval.

Thiomersal (thimerosal in the United States) is a preservative that is used in a range of children's vaccines and contains ethylmercury, an organic compound that is metabolized into mercury. High doses of a related organic mercury-containing compound methylmercury (MeHg) are toxic as shown after manmade disasters such as Minimata and Iraq.[1] However, there is also evidence that lower doses of MeHg can have adverse effects on childhood development if exposed in utero or in the early months of life. This stems from work-focused communities such as the Faroes,[2] who consume large quantities of fish and whale meat, although these findings have not been replicated in studies in the Seychelles among communities also dependent on fish.[1]

It has been suggested that low doses of ethylmercury might have a similar effect on childhood cognitive development as methylmercury; however, there is little evidence to support this claim.[3] Moreover, ethylmercury is more quickly metabolized and evacuated from the body than methylmercury.[4]

Current guidelines on safe exposure to thimerosal have been extrapolated from data on methylmercury and are varied, from 0.1 μg/kg/day of the Environ-

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mental Protection Agency in the United States to 0.47 μg/kg/day of the World Health Organization.[5] Before the change to thimerosal-free vaccines, US children could have been exposed to levels as high as 187.5 μg by the time they were 6 months of age, exceeding the Environmental Protection Agency guidelines. In the United Kingdom, the only vaccines that contain thimerosal and have been routinely used in the past 2 decades are whole-cell diphtheria/tetanus/pertussis (wDTP) vaccine or diphtheria-tetanus (DT) vaccine and any combination vaccine containing wDTP or DT. Although the United Kingdom exposure is lower by 6 months, the accelerated United Kingdom primary immunization schedule of 2/3/4 months means that a maximum exposure of 75 μg may be received by 4 months of age.

A recent US study[6] searched a large database of conditions linked to immunization history in young children and demonstrated a mild relationship between exposure to thimerosal and neurologic problems, including unspecified developmental delay, tics, attention-deficit disorder, and language and speech delay. The Institute of Medicine has stated that, although the hypothesis is biologically plausible, there is currently insufficient evidence to support a causal relationship and that more studies should be conducted to investigate this.[7] The current study was 1 of 2 British studies that were commissioned to provide additional information.

METHODS

Study Design

The Avon Longitudinal Study of Parents and Children (ALSPAC) enrolled women who resided in Avon in the southwest of England and had an expected date of delivery between April 1, 1991, and December 31, 1992. A total of 14 541 women were recruited; of these, 13 617 had singleton offspring surviving to 12 months of age. Additional details of the study aims and design are available (www.alspac.bris.ac.uk/).[8] Ethical approval was obtained from the study's own ethics committee and local research ethics committees.

Information on childhood behavior and development was collected in questionnaires administered regularly after the birth of the study child. Data presented here are derived from questions asked at 6, 18, 30, 47, 81, and 91 months of age. Information on potential confounders comes from questionnaires given to the mother during both pregnancy and the period that followed.

The information on immunizations was taken from the Bristol-based Child Health Surveillance Database (NHS Public Health Network). Preschool immunizations and examinations were recorded and monitored for all children who resided in the Avon area, and information available consists of date and type of immunization given.

Measures of Exposure

Mercury exposure for each child was defined according to the number of diphtheria/tetanus/pertussis (DTP) or DT doses received by 3 months (93 days) and by 4 months (124 days) of age. A continuous variable (HgAll) was also created from the age in days at DTP/DT doses 1, 2, and 3 in an attempt to calculate the age-specific DTP mercury exposure up to 6 months of age (see below).

HgAll = [(183 − age at dose 1) + (183 − age at dose 2) + (183 − age at dose 3)]/40

When a dose was given later than 183 days (6 months), this age was truncated to 183; hence, the contribution to the numerator from this immunization would be 0. The higher the value of HgAll, the earlier the 3 doses of DTP/DT were given and hence the greater the exposure to mercury at a young age. The denominator of 40 was chosen to achieve a score of between 0 and 10 solely to make the parameter estimates more sensibly scaled; however, before this scaling, 1 unit of the variable HgAll corresponded to a 1-day difference in the age at which DTP/DT was given. This measure is the same as that used by Andrews et al.[9]

Outcome Variables

Behavior Ratings

We used the Strengths and Difficulties Questionnaire (SDQ),[10] completed by the mother when the children were 47 and 81 months of age. The SDQ is a behavior scale that is used extensively in Europe and has been shown to have a good correlation with the Child Behavior Checklist.[11] The scale comprises 25 questions that are used to construct 5 subscales (prosocial, hyperactivity, emotional symptoms, conduct problems, and peer problems) and a total difficulties score (the total of all but the prosocial subscale that measures positive aspects of behavior). These scores have been prorated as instructed by their author[10]: no more than 2 missing items are permitted within each of the subscales, and no more than 8 missing items are permitted for the total difficulties score. Those children with a permitted number of missing values have their part-missing scores scaled up to make them comparable to the completely observed scores. The prosocial score differed from the others in that it was measuring positive behaviors. Hence, for this score, we use the low tail of the distribution as our binary outcome to indicate an adverse behavioral outcome.

Speech Problems and the Mother's Worries About Her Child's Speech

A number of questions have been examined regarding the child's speech as well as worries that the mother might have about speech from the 81-month questionnaire. 1) Does he or she stumble or get stuck on words or repeat them many times? (eg, I I I I want a sweet). 2) Does your child have difficulty in pronouncing certain sounds (eg, th, sss, t)? 3) Which aspects of your child's growth and development are you worried about—his/her speech? At 91 months, the mother was asked whether the child had ever had speech therapy.

Fine Motor Development

Fine motor skills were assessed using a scale based on the revised Denver Scale.[12] The items used were those from Denver II and were adapted for parental report with the study population after piloting and discussion with focus groups. These scores are administered when the children are ~6, 18, and 30 months of age and have been corrected for gestation and age of child when the questionnaire was completed; the age range has been restricted to an 8-week window around the 3 intended age points. The lower ~10% of the tail was taken to be the adverse developmental outcome

Tics

At 18, 30, and 42 months, we asked how often the child has a tic or twitch (weekly or more, less than weekly, or never). Because of the small number of cases, a variable was created showing whether any report of tics had been made over the 3 time points, giving a total of 171 cases. The question was asked again at 91 months; however, of the 167 children with tics at 91 months, only 11 had been reported as having tics in the period up to 42 months.

Special Needs

At 91 months, the mother was asked whether she had been informed, by the school or education authority, that her child had been designated as having special educational needs. She was also asked whether the child had been "statemented" (children are "statemented" when they have a learning difficulty or disability that affects their ability to function at school without the provision of extra resources; this category would include children, eg, with autism).

Confounders Used

The 9 confounders were as follows: birth weight (<2500 g, 2500 g+), gestation (<37 weeks, 37 weeks+), highest maternal educational attainment (3 groups created from a 5-point scale), gender, parity (first born, second born, third or more), housing tenure

(mortgaged, public housing, other-rented), midpregnancy maternal smoking (no, yes), child's ethnicity (white, nonwhite), and breastfeeding for 3 months or more. These are variously associated with childhood behavior and development. In addition, they all were related to the exposure variables at the 5% level of significance. Information was available on maternal fish consumption during pregnancy as a potential alternative source of mercury. It has previously been shown[13] that these measures are not positively associated with reduced child development; hence, these data were not used in the main analysis. The potential for a compounding of effects of thimerosal exposure and fish consumption was considered subsequently.

Statistical Methods

Distributions of outcome variables that comprised continuous data were heavily skewed and so were dichotomized because a transformation could not normalize the data. Each distribution was split such that the reference category contained ~80% to 90% of the data, with the upper tail (or lower for prosocial SDQ and Denver fine motor) constituting the adverse developmental outcome.

Unadjusted associations were assessed using a χ^2 test for trend with the continuous exposure measure being grouped in equal quartiles and the other 3 exposure variables treated as ordinal. After this, multivariable logistic regression models were derived with HgAll used in its continuous form and the other 2 exposures as ordinal variables.

RESULTS

Exposure Variables

Of the 13 617 eligible children, dates of immunization were available on all 3 doses for a total of 12 810. An additional 146 children who had a record of <3 doses but were known still to be living in Avon by the time they were 6 months of age (70 had no doses, 25 had 1 dose, and 51 had 2 doses) were included. As a result, exposure was known for a total of 12 956 subjects (see Fig 1 for a more detailed breakdown of the exclusions). None of the children in our sample of 12 956 had received influenza or hepatitis B vaccine (thimerosal-containing vaccines given to children in high-risk groups).

Doses by 3 Months

The distribution of number of doses obtained by 93 days was as follows: no doses, 527 (4.1%); 1 dose, 6586 (50.8%); and 2 or more doses, 5843 (45.1%).

Doses by 4 Months

For doses by 124 days, the distribution was as follows: no doses, 198 (1.5%); 1 dose, 1254 (9.7%); 2 doses 6675 (51.5%), and 3 doses; 4829 (37.3%). Thus, only 37% had achieved the third immunization by exactly 4 months of age. However, of those 6675 children with 2 doses by that time, 2118 received the third in the following week and another 1332 in the week after that. In fact, 5155 (77%) of them were fully immunized by the end of their fifth month.

Cumulative Dose

HgAll has a negatively skewed distribution with a median of ~6.5 units and a range of 0 to 10 units.

Outcome Variables and Unadjusted Results

The prevalence of each outcome along with the amount of data available (for which we also have exposure information) can be seen in the first 2 columns of Table 1. The reduction in sample size on adjustment shown in the final column was attributable mainly to the following confounders: breastfeeding (19.9% of 12 956 cases missing), maternal education level (16.6%), and child's ethnicity (13.5%). Other confounders suffered from up to 5% missing data.

Table 2 shows the unadjusted odds ratios for the 3 exposure variables and each of the outcomes. Confidence intervals are not shown. The following were significantly inversely associated at the 5% level with exposure by 93 days: hyperactivity at 47 months (P = .012), conduct problems at 47 months (P = .007), motor development at 6 months (P = .001) and at 30

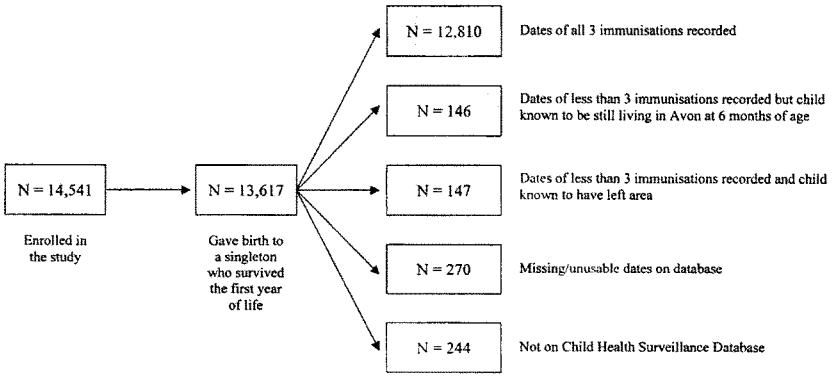

Fig 1. How the starting sample for the analysis was reached. The groups indicated by the 2 shaded boxes were believed to have valid thimerosal exposure data.

TABLE 1. Outcome Measures Used in Study of Effect of Exposure to Ethylmercury Measured in Children Delivered in Avon, UK, between 1991 and 1992

	% of Cases	*N* Unadjusted Sample	*N* Adjusted Sample
Behavior (47 mo)			
Prosocial	23.6	8858	7282
Hyperactivity	14.3	8862	7288
Emotional symptoms	10.5	8872	7290
Conduct problems	13.3	8857	7282
Peer problems	11.0	8871	7290
Total difficulties	15.4	8838	7268
Behavior (81 mo)			
Prosocial	19.2	7878	6610
Hyperactivity	11.0	7854	6602
Emotional symptoms	13.0	7871	6608
Conduct problems	10.6	7880	6612
Peer problems	14.6	7874	6608
Total difficulties	14.0	7851	6600
Fine motor skills			
6 mo	9.3	9788	8153
18 mo	11.0	9882	7969
30 mo	13.3	8522	6975
Speech			
Stumbles on words (81 mo)	17.8	7869	6597
Difficulty with sounds (81 mo)	13.6	7841	6573
Speech worries (81 mo)	3.3	7948	6654
Speech therapy (91 mo)	11.2	7346	6170
Tics			
Any tics (18–42 mo)	2.0	8256	6970
Tics (91 mo)	2.0	7495	6295
Special needs			
Child has special needs (91 mo)	8.4	7519	6310
LEA statement (91 mo)	2.9	7698	6441

LEA indicates Local Education Authority.

months ($P < .001$), difficulties with sounds at 81 months ($P = .014$), speech therapy at 91 months ($P = .024$), and special needs ($P = .038$) and statementing ($P = .013$) also at 91 months. All but speech therapy was found to be significant with both the 124-day exposure and HgAll with the inclusion of an additional association with conduct problems at 81 months ($P = .004$) for 124-day ($P = .016$) and for HgAll.

Multivariable Model

The results of the multivariable model are shown in Table 2. The combined effect of controlling for the 9 confounders was to remove a number of the significant negative associations found in the unadjusted analyses. However, this has proved insufficient to reverse the effect to the direction originally hypothesized.

There was only 1 (marginally) significant finding in the direction hypothesized: between poor prosocial behavior at 47 months of age and exposure by 3 months ($P = .031$); however, a single finding is to be expected given the 69 statistical tests performed. In 8 other analyses, the results were statistically significant but in the reverse direction, ie, the more exposed the infant, the more beneficial the outcome. These were doses by 3 months and conduct problems at 47 months ($P = .035$) and fine motor development at 30 months ($P = .021$); doses by 4 months and reported tics at 91 months ($P = .027$) and child with special educational needs ($P = .010$); and cumulative exposure and fine motor development at 30 months ($P = .003$), tics at 91 months ($P = .025$), special educational needs ($P < .001$), and child statemented by Local Education Authority ($P = .006$).

The size of the effects of each of the 9 potential confounding variables (birth weight, gestation, maternal education, gender, parity, housing tenure, midpregnancy smoking, child's ethnicity, and breastfeeding) on the relationship between exposure and outcome was examined. As an example, we studied the relationship between parity and exposure by 3 months of age. There was a strong inverse relationship with 54% of "only children" having had 2 or more doses by this time, 42% of those with 1 sibling and 34% of those with 2 or more siblings have the same exposure (χ^2 statistic for trend = 319.3, $P < .001$). Conversely, parity had the opposite relationship with fine motor development at 30 months. Ten percent of those with no siblings were in the lower tail, compared with 17% of those with 2 or more siblings (χ^2 statistic = 64.0, $P < .001$).

As a result, when controlling for parity in a model that examined the relationship between thimerosal exposure and fine motor development at 30 months, the odds ratio (OR) changed from 0.82 (confidence interval [CI]: 0.73–0.92; $P < .001$) to 0.87 (CI: 0.78–0.98; $P = .018$), thus reducing the apparent protective effect of thimerosal.

To investigate further, we chose 3 of the strongest unadjusted associations between the exposure and an adverse outcome in which to study the amount of confounding attributable to each of the 9 confounders. The pairs chosen were 1) conduct problems at 81 months and HgAll, 2) Denver development at 30

TABLE 2. Results of Regression Models With Exposure to Ethylmercury Defined by Dosage by 3 and 4 Months and a Cumulative Measure up to 6 Months and Measured in Children Delivered in Avon, UK, between 1991 and 1992

	Doses by 93 Days			Doses by 124 Days			HgAll		
	UOR	Adjusted Model		UOR	Adjusted Model		UOR	Adjusted Model	
		AOR	CI		AOR	CI		AOR	CI
Behavior (47 mo)									
Prosocial	1.02	1.12*	1.01–1.23	0.98	1.05	0.97–1.15	0.99	1.03	0.98–1.08
Hyperactivity	0.87*	0.91	0.81–1.03	0.88†	0.95	0.85–1.05	0.94*	0.98	0.93–1.04
Emotional symptoms	1.04	1.03	0.89–1.18	1.01	0.99	0.88–1.11	1.04	1.03	0.96–1.10
Conduct problems	0.86†	0.87*	0.77–0.99	0.90*	0.94	0.85–1.05	0.93†	0.96	0.90–1.01
Peer problems	1.06	1.06	0.93–1.22	1.04	1.07	0.95–1.21	1.02	1.02	0.96–1.09
Total difficulties	0.94	1.01	0.90–1.14	0.93	1.01	0.91–1.12	0.95*	0.96	0.94–1.05
Behavior (81 mo)									
Prosocial	0.98	0.97	0.87–1.09	0.95	0.97	0.88–1.07	0.98	0.99	0.94–1.04
Hyperactivity	0.97	0.98	0.85–1.13	0.97	1.01	0.89–1.15	0.97	1.00	0.93–1.07
Emotional symptoms	0.93	0.90	0.79–1.03	0.99	0.97	0.86–1.08	0.97	0.97	0.91–1.03
Conduct problems	0.92	0.93	0.80–1.07	0.86†	0.93	0.82–1.05	0.92†	0.95	0.90–1.02
Peer problems	1.03	1.04	0.92–1.18	1.01	1.03	0.92–1.15	0.99	1.01	0.95–1.07
Total difficulties	0.94	0.94	0.83–1.08	0.94	0.98	0.86–1.10	0.95	0.98	0.92–1.04
Fine motor skills									
6 mo	0.82†	0.97	0.84–1.11	0.88*	1.00	0.89–1.13	0.92†	0.99	0.93–1.05
18 mo	0.97	1.01	0.89–1.15	0.94	1.01	0.90–1.13	0.96	0.99	0.93–1.05
30 mo	0.82‡	0.86*	0.76–0.98	0.86†	0.92	0.82–1.02	0.90‡	0.92†	0.87–0.97
Speech									
Stumbles on words (81 mo)	0.95	0.93	0.83–1.05	0.96	0.99	0.90–1.10	0.97	0.99	0.94–1.05
Difficulty with sounds (81 mo)	0.87*	0.93	0.82–1.06	0.86†	0.91	0.82–1.01	0.93†	0.95	0.90–1.01
Speech worries (81 mo)	0.85	0.93	0.73–1.18	0.91	1.00	0.82–1.23	0.93	0.98	0.88–1.09
Speech therapy (91 mo)	0.86*	0.93	0.81–1.08	0.94	0.99	0.87–1.12	0.96	0.98	0.92–1.05
Tics									
Any tics (18–42 mo)	0.92	0.89	0.62–1.26	0.83	0.82	0.61–1.11	0.90	0.90	0.77–1.04
Tics (91 mo)	0.82	0.73	0.53–1.01	0.81	0.74*	0.57–0.97	0.90	0.87*	0.76–0.98
Special needs									
Child has special needs (91 mo)	0.86*	0.90	0.76–1.06	0.81†	0.84*	0.73–0.96	0.87‡	0.89‡	0.83–0.95
LEA statement (91 mo)	0.74*	0.78	0.60–1.02	0.81*	0.83	0.67–1.04	0.86†	0.87†	0.78–0.96

UOR indicates unadjusted odds ratio; AOR, adjusted odds ratio; LEA, Local Education Authority.
* $P < .05$.
† $P < .01$.
‡ $P < .001$.

months, and dosage by 3 months and 3) difficulty with sounds at 81 months and dosage by 4 months.

The unadjusted associations were recalculated for the complete-case sample for which we had all confounders. The effect size for 1 remained unchanged and for both 2 and 3 strengthened. Each confounder was then entered individually into a model that contained only the exposure variable, and the effect on the exposure's effect size was observed. The percentage change in the size of this effect was then studied to assess the amount of confounding that was taking place. We found that the only variable with a consistently high confounding effect was parity, with up to one third of the apparent effect of the exposure variable accounted for by this variable. Other than that, housing tenure and smoking accounted for 18% and 9.2% of the effect size, respectively, for example 1 and all other variables accounted for <5% each.

Missing Data

Outcome data were not available for all subjects. We compared the response to the 81-month questionnaire with the variable describing thimerosal exposure at 124 days of age. For our sample of 12 956, the response rate was 61.3%; however, this was strongly related to thimerosal exposure. Response rates ranged from 48% for those with no exposure by 124 days to 65.4% for those with full exposure (3 doses; χ^2 test for trend $P < .001$). A similar pattern was observed both for the other 2 exposure variables and for completion of other questionnaires used in this study.

A substantial number of cases were removed through inclusion of the 9 confounding factors. Additional investigation showed no evidence of a different unadjusted relationship for those cases for which only some of the confounders were observed.

To determine whether the 146 children with fewer than 3 doses of vaccine recorded were an atypical group, we refitted the multivariable models without these cases. The results were essentially the same.

Combined Effect of Fish Consumption and Thimerosal

Daniels et al[13] did not find an adverse association between maternal fish consumption during the third trimester of pregnancy and later neurodevelopment. In some cases, they actually observed a beneficial effect of increased fish in the diet, concluding that the nutritional contribution of fish might outweigh potentially harmful effects of methylmercury at the low levels present.

These findings are not dissimilar from our own results for thimerosal. This is all the more surprising when one considers that there is a negligible correlation between the 2 variables. For instance, 35.1% of those in the lowest quartile of the cumulative dose of

thimerosal by 6 months were in the top group of the fish variable (a composite measure of white and oily fish) used by Daniels et al, compared with 34.8% of those in the top quartile of cumulative dose.

We found in a bivariable analysis that it was not uncommon for both fish consumption and thimerosal to provide an independent beneficial effect. For instance, for conduct problems at 81 months of age, we found HgAll to give an OR of 0.92 (95% CI: 0.87–0.98) and fish to give an OR of 0.86 (95% CI: 0.80–0.92)—both exposures being used as 4-level ordinal variables with P values of .005 and <.001, respectively. In this particular example, fish remained marginally significant (OR: 0.92; 95% CI: 0.85–0.99; P = .033), whereas HgAll was not longer so (OR: 0.96; 95% CI: 0.89–1.02) once an adjustment for confounders had been made.

On the basis of the literature, one would expect that high levels of fish in pregnancy together with a high cumulative dose of thimerosal in early life would give an increased risk of neurodevelopmental delay compared with either factor in isolation. To investigate this, we created a 3-level variable. Group 1 was below the median of HgAll and scored low on fish intake, group 3 was above the median of HgAll and scored high on fish intake, and group 2 consisted of the middle ground. Table 3 shows the odds of each adverse outcome for groups 2 and 3 compared with that of group 1. We find that the odds are generally lower for group 3 than for group 2; furthermore, the odds for both groups are seldom >1. Hence, these 2 variables confer a combined benefit rather than a detriment.

DISCUSSION

This study, based on a large United Kingdom–based prospective cohort, shows no evidence of any harmful effect of an accelerated immunization schedule with thimerosal-containing vaccines. We are in agreement with the other British study[9] in showing little or no risk associated with the administering of thimerosal-containing vaccines to children younger than 6 months. Their 1 positive finding was a higher rate of tics; however, we showed no evidence of increased tics by 42 months and actually a reduction in reported tics at 91 months.

A reported limitation in the study by Andrews et al[9] was the lack of information on potential confounding variables. We have now shown that, with the variables we have considered at least, there is surprisingly little effect giving weight to their findings.

One explanation for the lack of a significant finding in our study is that the size of the effect of a confounder that has not been considered overwhelms any possible detrimental effect of thimerosal that one would expect to be acting in the opposite direction. This seems unlikely because many of the variables that we had expected to be strong confounders made very little difference to the results.

The analysis of the children with missing outcome data showed that these tended to be immunized later

TABLE 3. Combined Effect of Exposure to Methylmercury From Maternal Fish Consumption During Pregnancy and Exposure to Ethylmercury From Thiomersal During the First 6 Months of Life, Measured in Children Delivered in Avon, UK, between 1991 and 1992

	Unadjusted Effect		Adjusted Effect	
	Group 2, OR (95% CI)	Group 3, OR (95% CI)	Group 2, OR (95% CI)	Group 3, OR (95% CI)
Behavior (47 mo)				
Prosocial	0.87 (0.75–1.01)	0.86 (0.74–1.00)	0.86 (0.73–1.02)	0.94 (0.79–1.11)
Hyperactivity	0.96 (0.81–1.14)	0.70 (0.58–0.85)	1.08 (0.89–1.32)	0.90 (0.73–1.12)
Emotional symptoms	0.83 (0.68–1.01)	0.83 (0.67–1.01)	0.80 (0.65–1.00)	0.78 (0.62–0.99)
Conduct problems	0.77 (0.65–0.92)	0.63 (0.53–0.76)	0.83 (0.68–1.01)	0.76 (0.61–0.94)
Peer problems	0.88 (0.72–1.06)	0.82 (0.67–1.01)	0.92 (0.74–1.15)	0.94 (0.74–1.19)
Total difficulties	0.78 (0.67–0.93)	0.64 (0.54–0.76)	0.89 (0.73–1.07)	0.82 (0.67–1.00)
Behavior (81 mo)				
Prosocial	0.88 (0.74–1.04)	0.83 (0.70–0.99)	0.87 (0.72–1.05)	0.83 (0.68–1.01)
Hyperactivity	0.89 (0.73–1.10)	0.78 (0.63–0.97)	0.88 (0.69–1.11)	0.82 (0.64–1.06)
Emotional symptoms	0.81 (0.67–0.98)	0.83 (0.68–1.01)	0.78 (0.63–0.97)	0.80 (0.64–1.00)
Conduct problems	0.80 (0.65–0.99)	0.63 (0.51–0.79)	0.85 (0.67–1.07)	0.74 (0.58–0.95)
Peer problems	0.67 (0.56–0.81)	0.69 (0.58–0.84)	0.68 (0.56–0.84)	0.71 (0.58–0.88)
Total difficulties	0.76 (0.63–0.91)	0.66 (0.54–0.80)	0.80 (0.65–0.98)	0.74 (0.59–0.92)
Fine motor skills				
6 mo	0.89 (0.73–1.09)	0.82 (0.67–1.02)	0.93 (0.75–1.17)	0.98 (0.77–1.25)
18 mo	0.81 (0.68–0.97)	0.69 (0.57–0.84)	0.81 (0.66–0.99)	0.75 (0.60–0.94)
30 mo	0.88 (0.73–1.05)	0.73 (0.60–0.88)	0.88 (0.72–1.08)	0.77 (0.62–0.96)
Speech				
Stumbles on words (81 mo)	0.84 (0.71–1.00)	0.85 (0.71–1.01)	0.85 (0.70–1.04)	0.89 (0.72–1.08)
Difficulty with sounds (81 mo)	1.10 (0.90–1.34)	1.04 (0.84–1.28)	0.95 (0.76–1.19)	0.94 (0.75–1.19)
Speech worries (81 mo)	0.95 (0.65–1.38)	1.08 (0.73–1.58)	0.80 (0.53–1.20)	1.05 (0.69–1.60)
Speech therapy (91 mo)	0.80 (0.65–0.99)	0.74 (0.59–0.92)	0.73 (0.57–0.90)	0.73 (0.57–0.93)
Tics				
Any tics (18–42 mo)	0.70 (0.46–1.06)	0.41 (0.25–0.66)	0.98 (0.57–1.69)	0.55 (0.29–1.02)
Tics (91 mo)	0.97 (0.61–1.56)	0.77 (0.46–1.27)	1.01 (0.60–1.70)	0.70 (0.40–1.24)
Special needs				
Child has special needs (91 mo)	0.86 (0.68–1.10)	0.82 (0.64–1.05)	0.80 (0.61–1.05)	0.81 (0.62–1.08)
LEA statement (91 mo)	0.75 (0.52–1.10)	0.59 (0.40–0.89)	0.77 (0.52–1.16)	0.64 (0.41–1.00)

LEA indicates Local Education Authority.

and hence have a lower thimerosal exposure at any given age. We also found that for the nonmissing data, those who were immunized later tended to have the kind of sociodemographic status that was associated with the poor developmental outcomes. This means that the children with missing outcome data are likely to have lower thimerosal exposure but more adverse outcomes. Therefore, any bias introduced as a result of not having the missing data is likely to be in the direction of the hypothesis (higher exposure associated with adverse outcomes). Although this bias would be expected to effect the unadjusted analysis, it should have much less effect on the adjusted analysis that controls for sociodemographic factors. Although it could be argued that scores based on maternal reported behavior/development are not sensitive enough to detect the subtle differences that we might expect in a population with no other major sources of mercury, we have shown that there is also no detrimental effect with the less subjective measure of a child's having special educational needs.

One limitation of this study is the uniformity in the exposure variable. As stated earlier, 77% of those who had had only 2 doses by 4 months of age had received their third vaccine by the end of the fifth month. We would expect this to reduce our power to detect a harmful effect of the thimerosal preservative; however, this does not explain why 5 of the 6 significant results and 39 of the 57 nonsignificant results are in the direction contrary to that hypothesized.

CONCLUSION

We could find no convincing evidence that early exposure to thimerosal had any deleterious effect on neurologic or psychological outcome when given according to an accelerated schedule. This is reassuring for developing countries that receive DTP vaccines according to the Expanded Program of Immunization schedule and where multidose vials that contain the thimerosal preservative are often the only option. In the face of the current evidence from this study and the growing literature, the dangers posed by contaminated multidose vaccine vials far outweigh any potential risk posed by thimerosal.

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Thimerosal Exposure in Infants and Developmental Disorders: A Retrospective Cohort Study in the United Kingdom Does Not Support a Causal Association

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ABSTRACT. *Objective.* **After concerns about the possible toxicity of thimerosal-containing vaccines in the United States, this study was designed to investigate whether there is a relationship between the amount of thimerosal that an infant receives via diphtheria-tetanus-whole-cell pertussis (DTP) or diphtheria-tetanus (DT) vaccination at a young age and subsequent neurodevelopmental disorders.**

Methods. **A retrospective cohort study was performed using 109 863 children who were born from 1988 to 1997 and were registered in general practices in the United Kingdom that contributed to a research database. The disorders investigated were general developmental disorders, language or speech delay, tics, attention-deficit disorder, autism, unspecified developmental delays, behavior problems, encopresis, and enuresis. Exposure was defined according to the number of DTP/DT doses received by 3 and 4 months of age and also the cumulative age-specific DTP/DT exposure by 6 months. Each DTP/DT dose of vaccine contains 50 μg of thimerosal (25 μg of ethyl mercury). Hazard ratios (HRs) for the disorders were calculated per dose of DTP/DT vaccine or per unit of cumulative DTP/DT exposure.**

Results. **Only in 1 analysis for tics was there some evidence of a higher risk with increasing doses (Cox's HR: 1.50 per dose at 4 months; 95% confidence interval [CI]: 1.02–2.20). Statistically significant negative associations with increasing doses at 4 months were found for general developmental disorders (HR: 0.87; 95% CI: 0.81–0.93), unspecified developmental delay (HR: 0.80; 95% CI: 0.69–0.92), and attention-deficit disorder (HR: 0.79; 95% CI: 0.64–0.98). For the other disorders, there was no evidence of an association with thimerosal exposure.**

Conclusions. **With the possible exception of tics, there was no evidence that thimerosal exposure via DTP/DT vaccines causes neurodevelopmental disorders.** *Pediatrics* **2004;114:584–591;** ***cohort study, neurodevelopment, safety, thimerosal, thiomersal, vaccines.***

ABBREVIATIONS. Hg, mercury; WHO, World Health Organization; VSD, Vaccine Safety Datalink; CDC, Centers for Disease Control and Prevention; HMO, health maintenance organization; ADD, attention-deficit disorder; GPRD, General Practice Research Database; ICD, *International Classification of Diseases*; DTP, diphtheria-tetanus-whole-cell pertussis; DT, diphtheria, tetanus; GP, general practitioner; HR, hazard ratio; CI, confidence interval.

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Inorganic mercury (Hg) poses a potential risk of neurodevelopmental and renal toxicity in young children.[1,2] Cumulative exposure to an organic mercury–containing compound, methylmercury, can also produce neurologic or renal damage as it has a long half-life and can cross the blood-brain barrier, where it accumulates and is converted to inorganic mercury. Guidelines to limit cumulative exposure to methylmercury have been drawn up by various agencies and incorporate a wide margin of safety. The maximum daily dose specified by these different agencies varies by nearly 5-fold, the most stringent being the guideline of the Environmental Protection Agency in the United States that specifies a maximum daily exposure to Hg of 0.1 μg/kg extrapolated from data on methylmercury exposure. These guidelines are reproduced by Pichichero.[2]

Ethylmercury, a related organic mercury compound, is a constituent of thimerosal, an antibacterial agent used in certain nonlive vaccines. Ethylmercury has a much shorter half-life than methylmercury, being rapidly excreted via the stools after parenteral administration such that blood levels remain substantially below the safe threshold.[2] Nevertheless, the guidelines to limit cumulative methylmercury exposure have been translated to ethylmercury.[3] In the United States, increases during the 1990s in the number of childhood vaccines that contained thimerosal, which contains 49.6% Hg by weight, led to questions about safety because the maximum cumulative exposure in some US children was 187.5 μg Hg by 6 months of age, which would have exceeded the stringent Environmental Protection Agency limit. Although there is no evidence that this level of Hg exposure via ethylmercury was likely to or had actually caused any harm, a joint statement was issued by the American Academy of Pediatrics and the Public Health Service in 1999 recommending the removal of thimerosal from vaccines as soon as possible, as a precautionary measure.[4] Although the World Health Organization (WHO) supported in principle the move toward thimerosal-free vaccines, it nevertheless recommended that vaccines that contain thimerosal continue to be used in the meantime because the

known morbidity and mortality from vaccine-preventable diseases greatly outweighed any theoretical risk from ethylmercury.[5]

In 2001, the preliminary results of an unpublished US cohort study that screened for associations between various neurodevelopmental and renal disorders and infant thimerosal exposure in vaccines were made available to an Institute of Medicine Immunization Safety Review.[6] This study used the computerized Vaccine Safety Datalink (VSD) developed by the Centers for Disease Control and Prevention (CDC) in association with 2 health maintenance organizations (HMOs).[7] The preliminary results suggested a possible trend between the level of ethylmercury exposure in the first few months of life and the following neurodevelopmental diagnoses: tics, attention-deficit disorder (ADD), language/speech delays, unspecified delays, and general neurodevelopmental delays. Although additional analyses were later conducted to control for confounding variables and to include more data, some disorders remained significant. Given the exploratory nature of this study, it was unclear whether these findings were real, a result of chance, or a result of uncontrolled confounding or bias. A subsequent, much smaller study by the CDC using another HMO data set did not confirm the first findings but had inadequate power to identify effects of the size seen in the first study.[6]

After review of the available evidence by the WHO Global Advisory Committee on Vaccine Safety, it was recommended that other studies be conducted to test the hypotheses raised by the VSD study.[8] The General Practice Research Database (GPRD) in the United Kingdom was identified as 1 of the few databases that were comparable to the HMO databases used in the VSD study.[9,10] In addition, the Avon Longitudinal Study of Pregnancy and Childhood in the United Kingdom was identified as a prospective cohort with information on vaccination and regular assessment of children's developmental progress. This cohort had the advantage of having data on many potential confounding variables, although it was not large enough to assess rare outcome conditions. The results of the analysis of this study are published together with this article.[11]

The GPRD holds data on all significant patient consultations, referrals, and prescribed medicines, including vaccines from 1988 from ~500 general practices in the United Kingdom. Together, these practices provide primary health care for 3.4 million patients (5.7% of the population). Preliminary analyses conducted by staff of the Morbidity and Health Care Team of the Office for National Statistics (which until 1999 managed the GPRD) using the *International Classification of Diseases* (ICD) codes for the outcomes of interest from the CDC study confirmed that the GPRD had sufficient power to test the hypotheses generated in the CDC study

In the United Kingdom, the only vaccine that contains thimerosal and has been used routinely in the infant immunization program in the past 2 decades is diphtheria-tetanus-whole-cell pertussis (DTP) vaccine or diphtheria-tetanus (DT) vaccine and any combination vaccine that contains DTP or DT. These vaccines all contain 50 μg of thimerosal (25 μg of Hg) per dose. No other thimerosal-containing vaccines have been given routinely to United Kingdom children, so the cumulative Hg exposure by age can be readily obtained from the number of doses of DTP- or DT-containing vaccines given. Because the United Kingdom changed to an accelerated 2/3/4 month DTP immunization schedule in 1990 (replacing the former 3/5/10 month schedule) and because vaccinations are generally given on time in the United Kingdom, a substantial proportion of children in the GPRD cohort will have had a cumulative Hg exposure of 150 μg of thimerosal (75 μg of Hg) by 4 months of age. This level of Hg exposure, although lower than the maximum of 187.5 μg received in the United States by 6 months of age, is similar to the level received by ~3 to 4 months of age in the United States. It is also the same as the amount of thimerosal used by developing countries that follow the expanded immunization schedule.

METHODS

The GPRD Cohort

Information on all children who were born from 1988 to 1997 and had at least 2 years of continuous follow-up from birth in the GPRD was obtained from the Office for National Statistics. Data were available up to the end of 1999 in linked patient, medical, and prevention databases for 152 898 children. For quantifying thimerosal exposure by age, it was important that an exact date of birth (to the day) be available. The patient database had information only on year and month of birth, but we were able to obtain exact dates of birth for 109 863 children from the date at which procedures or measurements taken on the day of birth were recorded in the linked medical database. Additional data quality processing, mostly concerning the validity of the dates of birth, vaccination, or the date of recording of the neurodevelopmental problems, led to the exclusion of 2711 records (2.5% of the cohort), leaving 107 152 children for analysis (Fig 1).

For each child, information was available on date of birth, gender, date leaving the practice (if applicable), last date that data were obtained from the practice, dates of all vaccinations (along with vaccine code and dose number), and dates and Read or OXMIS codes for all medical events. Read and OXMIS are diagnostic coding schemes that are built into practice software and based respectively on ICD-9 and ICD-8 codes. We had no information enabling identification of the patient and no information on general practitioner (GP) practice, so the only potential confounding variables that could be allowed for were gender and year/month of birth.

Exclusion Criteria

Children with Read and OXMIS codes relating to a variety of prenatal, perinatal, and postnatal conditions that occurred before 6 months of age were excluded as were children who were recorded as having an outcome event in the first 6 months of life. These children were excluded from the main analysis because the presence of such a condition is likely to affect both vaccination and future neurodevelopmental outcomes. Examples of exclusions were birth asphyxia, Down syndrome, cerebral palsy, meningitis, encephalitis, and head injury. Children were also excluded when they received either hepatitis B or influenza vaccination in the first 6 months of life because such children are likely to be an atypical subgroup. Children who were born preterm (<37 weeks' gestation) are likely to be of low birth weight, and many stay small. Such infants might be more susceptible to standard doses of thimerosal. Preterm infants therefore were analyzed separately.

Exposure Variables

Hg exposure for each child was defined according to the number of DTP/DT doses received at 3 months (93 days) and 4 months

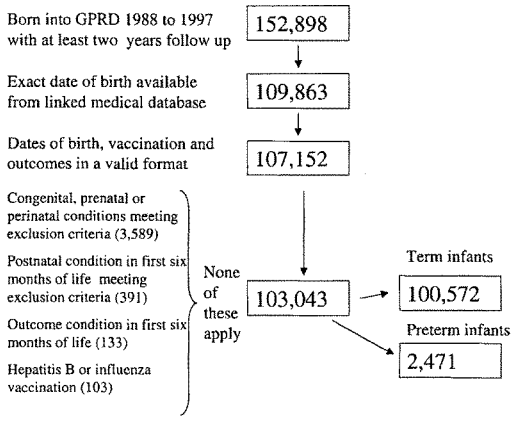

Fig 1. Selection of the GPRD cohort.

(124 days) of age. These ages were chosen to give a wide distribution for the number of children who received 0 to 3 doses of DTP/DT. A continuous variable (HgAll) that aimed to capture the age-specific Hg exposure up to 6 months (183 days) of age was also created. This variable was created to circumvent the problem of choosing age cut-offs and also to provide greater study power. HgAll was created from the age in days at the 3 DTP/DT doses as follows:

HgAll = [(183 − age at dose 1) + (183 − age at dose 2) + (183 − age at dose 3)]/40

When a dose was not given or was given later than 183 days of age, for the purpose of the above calculation, the age was set to 183 days. The higher the value of HgAll, the earlier the 3 doses of DTP/DT were given and the child thus was exposed to a higher dose of mercury at a younger age. The arbitrary division by 40 was to ensure that when calculating hazard ratios (HRs), 1 unit of HgAll was of a meaningful size. One unit of HgAll corresponds to a combined difference of 40 days (while under the age of 183 days) in the age at which DTP/DT is given. For example, a child who received dose 1 at 60 days, dose 2 at 88 days, and dose 3 at 116 days would have an HgAll value of 7.125, whereas a child who received doses 1 and 2 by the same age but dose 3 at 156 days would have an HgAll value of 6.125.

Outcome Events

The outcome events of most interest were OXMIS and Read codes relating to general neurodevelopmental disorders (a composite category that comprised the following ICD-9 codes: 299 [childhood psychoses including autism], 300.3 [obsessive-compulsive disorders], 307 [specific psychopathological syndromes], 312.0 [unsocialized disturbance conduct, aggressive], 313 [emotional disturbance], 314 [hyperkinetic syndrome], 315 [specific delays in development], 317–319 [mental retardation], and V40 [mental and behavioral problems]) and other individual conditions as follows: unspecified development delays, tics, ADD and language or speech delay, enuresis, encopresis, autism, and nonspecific behavioral problems. The ICD-9 codes relating to these outcomes are shown in Table 1.

Statistical Methods

The data were analyzed by Cox proportional hazards survival analysis in the statistical package S-Plus.[12] Survival for each child was taken as the number of days from age 183 days to the age at the first mention of each predefined outcome of interest. If for a particular outcome no event occurred, then survival was taken as being greater than the time to the end of follow-up. HRs with 95% confidence intervals (CIs) and two-sided P values were calculated for the effect of thimerosal exposure. The effect of the number of doses received by 3 and 4 months of age was quantified by the trend in hazard per dose. When the trend was significant, the HRs for 1, 2, and 3 doses at 4 months compared with the baseline of 0 doses were also calculated. A HR >1 is consistent with the hypothesis that early Hg exposure is associated with an increased risk of a predefined developmental outcome, whereas a HR <1 is

TABLE 1. Numbers With the Various Outcome Conditions for the Term and Preterm Cohorts, the Percentage Male, and the Estimated Median Age in Years at First Mention

Outcome (ICD-9 Codes)	Term Infants			Preterm Infants		
	n	% Male	Median age at First Mention, y	*n*	% Male	Median age at First Mention*, y
General developmental disorders	2035	71.1	3.6	110	66.4	3.6
Unspecified behavioral problem (3129)	816	71.2	4.8	30	70.0	5.3
Enuresis (7883)	1312	53.6	5.6	35	60.0	6.1
Encopresis (7876)	121	66.9	5.5	4	75.0	—
Tics (3072)	70	70.0	5.2	1	100.0	—
ADD (314)	222	77.0	3.7	8	87.5	—
Language/speech (3153)	666	70.4	3.0	33	69.7	3.4
Unspecified delay (3159)	485	67.2	2.4	52	59.6	2.1
Autism (2990)	104	89.4	4.4	2	50.0	—

* Where there are <10 cases, a median age is not calculated

TABLE 2. Distribution in the Term and Preterm Cohorts of the Number of Doses of DTP/DT Received in Total, by 3 and 4 Months of Age

Exposure	Level	Term Cohort		Preterm Cohort	
		n	%	*n*	%
No. of doses of DTP/DT	0	945	0.9	37	1.5
	1	1687	1.7	38	1.5
	2	1090	1.1	60	2.4
	3 (third dose ≤ 1 y)	94730	94.2	2255	91.3
	3 (third dose >1 y)	2120	2.1	81	3.3
Doses by age 3 mo	0	7881	7.8	350	14.2
	1	51309	51.0	1390	56.3
	2	41382	41.1	731	29.6
Doses by age 4 mo	0	3419	3.4	142	5.8
	1	11766	11.7	442	17.9
	2	50349	50.1	1299	52.6
	3	35038	34.8	588	23.8

indicative of a potential protective effect. In all analyses, gender and year of birth were included as potential confounding factors; month of birth was also included when statistically significant at a 5% level. The effect of the number of doses of thimerosal was also examined visually in reverse Kaplan-Meier plots.

The main analysis included all children whether recorded as receiving 0, 1, 2, or 3 doses of DTP/DT at any age. However, it seemed possible that, as a result of socioeconomic or other confounding factors, children who did not complete vaccination in the first year of life would form a biased group. The data therefore also were analyzed after excluding all children who did not receive 3 doses of vaccination by age 366 days.

The median age at first mention of each outcome (Table 1) was estimated by taking the proportion of those who were followed up for 8 years or more with an event by 8 years (eg, 3.33% of 7195 followed up for at least 8 years had a general developmental disorder) and then finding the age by which half of this proportion had had an event (eg, 1.67% of 63 466 followed up for 3.6 years or more). This method of estimating the median age was used to adjust for the effect of censored data but is still conditional on the event occurring by the age of 8.

Validation

Validation of GP notes could be performed only for those GP practices that were still participating in the GPRD and with the case still registered. Validation was performed by sending a questionnaire to the GP asking for confirmation and additional details of the diagnosis and any subsequent related consultations and also the vaccination history, date of birth, and gender. Copies of relevant patient notes were also requested. Validation was sought for all cases of tics for whom validation was possible (36 of the 71 cases) as well as a random subset of 30 with ADD, 40 with language or speech delay, 30 with unspecified developmental delays, and also an additional 30 in the general developmental delay category not covered by the above.

RESULTS

Cohort Selection

Details of the selection of the cohort of 103 043 children are given in Fig 1. The average length of follow-up in the cohort was 4.7 years (range: 2–11). Only 7.3% had a follow-up of longer than 8 years, reflecting that fewer practices contributed to the GPRD from 1988 to 1990.

Exposure

More than 96% of term children eventually received all 3 doses of DTP/DT (Table 2). By 4 months of age, most children had received 2 or 3 doses; however, there was sufficient variability in the number of doses received to enable fairly precise estimates of the trend in the HR per dose for the various outcomes. Preterm children were less vaccinated and received vaccination later than term children.

Figure 2 shows the distribution of HgAll for the term cohort. The median value (interquartile range) of HgAll is 6.5 (4.5–7.0) in the term cohort and 6.1 (4.7–6.8) in the preterm cohort. Although few children received vaccinations early (HgAll >7.5), many got the 3 doses close to the correct time (HgAll: 6.5–7.5). Short delays in receiving the 3 doses were fairly common. However, relatively few children received <3 doses or got the vaccine very late.

Outcomes

All of the neurodevelopmental disorders investigated were more common in boys than in girls (Table 1). They also occurred more often in preterm children, with general developmental disorders occurring in 4.5% of preterm children and 2.0% of term children. The estimated median age of first mention of the disorders in term children varied from 2.4 years for unspecified delays to 5.6 years for enuresis. The age at first mention was similar for the term and preterm cohorts. Other than the general developmental disorders category, the most common disorders were enuresis, behavioral problems, and language/speech delays.

Risk Estimates

Table 3 shows the adjusted HRs per DTP/DT dose or HgAll unit for the various disorders. There were apparent protective effects from DTP/DT exposure for general developmental disorders, ADD, and unspecified developmental delay. The only evidence of a greater hazard with increasing thimerosal exposure was for tics, and this was significant only in the analysis that excluded children who did not receive 3 doses by 1 year of age. For the other disorders, exclusion of children who did not receive 3 doses by age 1 did not substantially affect the HRs; for example, the HR per dose at age 4 months was 0.86 (95% CI: 0.81–0.92) for general developmental disorders.

In the preterm cohort, none of the HRs was significantly different from 1 (data not shown). This cohort was not large enough to have the power to identify small effects; however, the direction of the effects was similar to the term cohort. For example, for

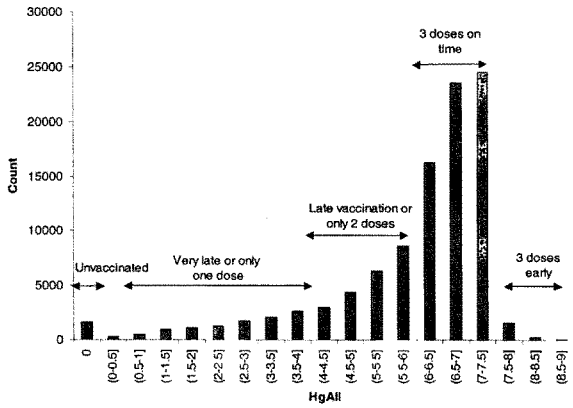

Fig 2. Distribution of the HgAll variable in the term cohort.

TABLE 3. HR for Various Neurodevelopmental Disorders According to the Number of Doses of DTP/DT Received by 3 and 4 Months of Age and the Age-Specific Cumulative Exposure HgAll in the Term Cohort

Outcome	Doses by 3 Months			Doses by 4 Months			HgAll		
	HR* Per Dose	95% CI	*P* Value	HR Per Dose	95% CI	*P* Value	HR Per Unit	95% CI	*P* Value
General developmental disorders	0.87	0.81–0.93	<.001	0.89	0.84–0.94	<.001	0.95	0.92–0.97	<.001
Behavioral problem	0.97	0.87–1.08	.55	0.98	0.90–1.07	.68	0.98	0.94–1.02	.36
Enuresis	1.07	0.98–1.17	.13	1.04	0.97–1.12	.25	1.02	0.98–1.05	.29
Encopresis	0.81	0.61–1.07	.13	0.82	0.65–1.02	.074	0.92	0.84–1.02	.11
Tics	1.45	0.99–2.15	.059	1.34	0.96–1.85	.082	1.14	0.97–1.35	.11
Tics†	1.62	1.05–2.50	.031	1.50	1.02–2.20	.035	1.33	1.06–1.69	.015
ADD	0.79	0.64–0.98	.033	0.82	0.70–0.97	.022	0.90	0.84–0.97	.004
Language or speech delay	0.89	0.79–1.01	.070	0.96	0.87–1.06	.38	0.99	0.94–1.03	.56
Unspecified developmental delay	0.80	0.69–0.92	.002	0.84	0.75–0.94	.002	0.91	0.86–0.95	<.001
Autism	0.89	0.65–1.21	.46	0.94	0.73–1.21	.66	0.99	0.88–1.12	.89

* Adjusted for gender, year of birth, month of birth (general developmental disorders only).
† Results from the analysis that excluded those who did not receive 3 doses of DTP/DT by 366 days.

general developmental disorders, the HR per doses at 4 months was 0.80 (95% CI: 0.63–1.00). There was no evidence that the higher exposure by body mass in preterm children gave an increased risk of neurodevelopmental problems.

Table 4 shows the HRs of 1, 2, and 3 doses by 4 months of age compared with the baseline of 0 doses for variables with a significant trend by dose. The results show that for general developmental disorders, ADD, and unspecified delay, there is a decreasing trend by dose. For tics, the effect is less clear, with the main difference being the lower hazard at 1 dose. Reverse Kaplan-Meier plots show these results in more detail (Fig 3).

The 4109 children who were dropped as a result of the initial exclusion criteria were examined in a separate analysis. As with the premature children, they had a lower DTP/DT exposure than the main cohort and also a greater risk of outcome events. As with the term cohort, this group showed a protective DTP/DT effect for general developmental disorders with a HR for the trend in doses by 4 months of age of 0.84 (95% CI: 0.72–0.97).

Validation

From the validation exercise, responses were received from 162 of 166 general practices. Of these, 10 could not provide any information. Of the remaining 152, 122 (80%) confirmed that the child presented with the given condition, 11 (7%) stated that the diagnosis reflected only parental concern, 11 (7%) had the diagnosis incorrectly coded, and in 8 (5%) no record of the diagnosis or subsequent episodes could be found in the notes. Of the 122 with a confirmed diagnosis, 48 were transient problems, 31 were long term, and for 43, the duration could not be determined. For tics, responses were received for all 36, of whom the duration of symptoms could be determined in 27. In 24 (89%) of 27, the tic was only a transient problem. In 3 cases, tics was recorded when in fact the individual presented with a parasitic tick. The validation confirmed that the dates of vaccina-

TABLE 4. Effect of Number of DTP/DT Doses Received by 4 Months of Age on Outcomes With Significant Associations in the Trend Analysis for the Term Cohort

Outcome	DTP/DT Doses by Age 4 Months	No. With Outcome	HR*	95% CI
General developmental disorders	0	86	1.00	Reference
	1	302	0.99	0.78–1.25
	2	1028	0.85	0.68–1.06
	3	619	0.75	0.60–0.94
Tics	0	3	1.00	Reference
	1	2	0.17	0.03–1.04
	2	40	1.14	0.35–3.73
	3	25	1.12	0.34–3.77
Tics†	0	0	0.00	Not estimable
	1	2	0.18	0.04–0.76
	2	38	0.98	0.58–1.62
	3	25	1.00	Reference
ADD	0	15	1.00	Reference
	1	34	0.62	0.34–1.14
	2	105	0.49	0.29–0.85
	3	68	0.47	0.27–0.83
Unspecified developmental delay	0	20	1.00	Reference
	1	85	1.20	0.74–1.96
	2	234	0.80	0.51–1.26
	3	146	0.73	0.46–1.16

* Adjusted for gender, year of birth, and month of birth (general developmental disorders only).
† Results from the analysis that excluded those who did not receive 3 doses of DTP/DT by 366 days.

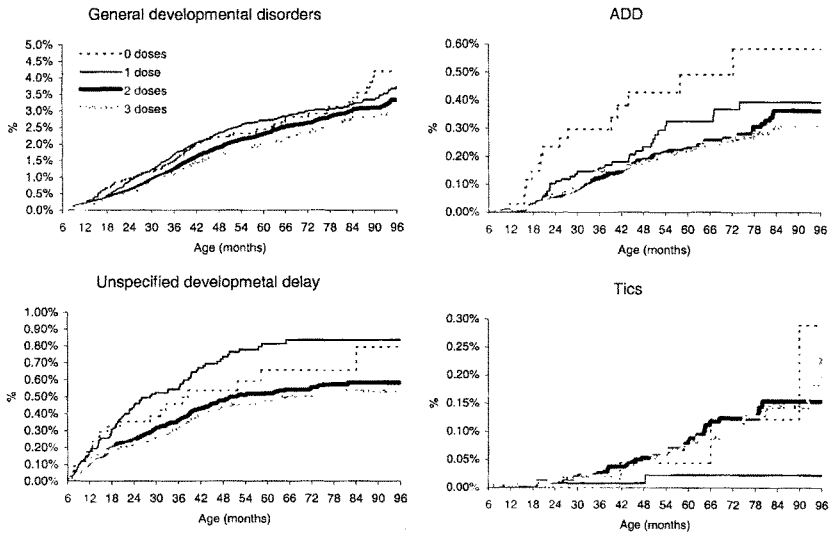

Fig 3. Cumulative percentage of children with general developmental disorders, ADD, unspecified developmental delays, and tics from 6 months to 96 months of age, stratified according to DTP/DT doses received by 4 months of age. Plots are derived from the inverse of the Kaplan-Meier survival curves and take account of variable follow-up times in individuals.

tion were accurate and that the dates of the events recorded in the GPRD were correct or close to the date noted in the GP record.

DISCUSSION

With the possible exception of tics, there was no evidence of an increased risk of various neurodevelopmental disorders with increasing thimerosal exposure at a young age via DTP/DT vaccination in the United Kingdom. For general developmental disorders, unspecified developmental delay, and ADD, there was an apparent protective effect from increasing thimerosal exposure. These outcomes all had a median age at first mention at a relatively young age

and therefore were more likely to be affected by confounding factors that are also associated with delayed or incomplete vaccination. Outcome conditions first mentioned when the child was older did not show any evidence of an association with DTP/DT dosage, with the exception of the apparent higher risk of tics in 1 analysis.

Although we were able to make some exclusions on the basis of medical events in the first 6 months of life, a limitation of our study was the inability to adjust for many potential confounding factors, such as unrecorded medical conditions and socioeconomic factors. The longitudinal United Kingdom study, published with this article,[11] did have information available on potential confounding variables. In that study, early thimerosal exposure generally showed no association or was protective. The size of the protective effects reduced when controlling for confounding variables, although the changes were small. This suggests that additional adjustment for confounding in the GPRD study would have a relatively small effect.

Our study has many similarities to the US VSD study and, with the exception of tics, does not confirm the hypotheses raised by the preliminary analysis of that study. Both studies were cohort studies with limited adjustment for confounding. The main difference was the lower total thimerosal exposure in the United Kingdom. It should be noted, however, that the exposure in the United Kingdom by 4 months of age was similar to the United States by the same age; however, in the United States, exposure increased further from 4 to 7 months. If the increased risk in the US study were attributable only to the additional thimerosal exposure after 4 months of age, then it is possible that our study may not have been able to detect the risks found in the US study. In the final analysis of the US cohort study,[13] which had a longer follow-up time and separate analyses for each of the 2 HMOs and also controlled for other variables including health care–seeking behavior, the only variables that remained significant were tics in 1 HMO and language delay in the other. Therefore, many of the preliminary results from the US study were probably attributable to confounding or chance.

The validation exercise confirmed most diagnoses with only 7% of the sample validated deemed incorrectly coded. An additional 13% were questionable because they reflected only parental concern or could not be located in the notes. This lack of specificity is a limitation of the study because it biases against finding an association. If we assume that a conservative 20% of cases have a false diagnosis and that there is a true HR per dose of 1.20, then this bias will result in a slightly lower observed HR of 1.15. Other validation exercises undertaken using the GPRD have found clinical diagnoses to be accurate.[14–16] The predominance of boys as well as the median age at first mention was as expected for the various conditions[17] and provides a degree of validation.

The question remaining is whether there could be a true effect of thimerosal exposure on tics. Evidence supporting a true effect is that it was significant in the US study and in a secondary analysis in the GPRD study; however, there are many reasons to doubt that there is a true effect. First, the US study was a screening study that looked at many outcomes; the borderline significance in 1 HMO of tics merely raised the question. Second, although the GPRD study gave a borderline significant association, the Avon longitudinal United Kingdom study showed no evidence of a relationship between thimerosal exposure and tics or twitches despite that this outcome was reported for ~150 children. Third, the validation exercise revealed that the vast majority of tics were minor transient events. Finally, no other developmental outcomes were found to be associated with thimerosal exposure, contrary to what would be expected if there were a true effect on tics. Although the possibility of a true effect of thimerosal on minor transient tics cannot be ruled out, it is more plausible that the association found is a chance effect or the result of confounding.

Other than the US VSD study, the only other published cohort study that has assessed exposure to thimerosal-containing vaccines and any of the outcomes that we looked at is a study in Denmark that looked at autism.[18] The thimerosal exposure in this study was 25 μg of Hg at 5 weeks, then 50 μg of Hg at 9 weeks and 10 months. As with our study, the authors found no evidence of an association.

A recent study that measured Hg levels in blood and excretion via the stools and urine in term infants who received vaccines that contained thimerosal[2] found no evidence of a rise in blood concentrations above "safe values" and showed that Hg in ethylmercury is eliminated rapidly via the stools. This provides additional evidence that 3 doses of DTP given at monthly intervals does not present an Hg-related risk for neurodevelopmental disorders.

The results of the 2 United Kingdom studies were presented to the WHO Global Advisory Committee on Vaccine Safety in June 2002.[8] These studies contributed to the conclusion that there is currently no evidence of mercury toxicity in infants, children, or adults who are exposed to thimerosal in vaccines and that there is no reason to change current immunization practices with thimerosal-containing vaccines on grounds of safety. This conclusion is particularly important for developing countries that administer thimerosal-containing DTP vaccines according to the expanded immunization schedule.

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TWO MINORITIES SPUR RAPID U.S. GROWTH

"Explosive growth among Hispanic and Asian-Americans propelled a surge in the United States population from 2000 to 2003 to nearly 300 million people, the Census Bureau reported on Monday. The number of people of Hispanic descent, the nation's largest minority group, rose to 39.9 million, a 13 percent increase from April 2000 to July 2003, the agency said. That far outpaced the 3 percent increase in the American population during the same time, to 290.8 million. Asian-Americans were the next fastest growing among the large minority groups, up 12.6 percent, to 11.9 million, while the black population rose nearly 4 percent, to 37 million. About 4.3 million people listed themselves as of more than one race, up 10.5 percent from 2000."

Associated Press. *New York Times.* June 15, 2004

Noted by JFL, MD

Thimerosal-Containing Vaccines and Autistic Spectrum Disorder: A Critical Review of Published Original Data

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ABSTRACT. *Objective.* **The issue of thimerosal-containing vaccines as a possible cause of autistic spectrum disorders (ASD) and neurodevelopmental disorders (NDDs) has been a controversial topic since 1999. Although most practitioners are familiar with the controversy, many are not familiar with the type or quality of evidence in published articles that have addressed this issue. To assess the quality of evidence assessing a potential association between thimerosal-containing vaccines and autism and evaluate whether that evidence suggests accepting or rejecting the hypothesis, we systematically reviewed published articles that report original data pertinent to the potential association between thimerosal-containing vaccines and ASD/NDDs.**

Methods. **Articles for analysis were identified in the National Library of Medicine's Medline database using a PubMed search of the English-language literature for articles published between 1966 and 2004, using keywords thimerosal, thiomersal, mercury, methylmercury, or ethylmercury alone and combined with keywords autistic disorder, autistic spectrum disorder, and neurodevelopment. In addition, we used the "related links" option in PubMed and reviewed the reference sections in the identified articles. All original articles that evaluated an association between thimerosal-containing vaccines and ASD/NDDs or pharmacokinetics of ethylmercury in vaccines were included.**

Results. **Twelve publications that met the selection criteria were identified by the literature search: 10 epidemiologic studies and 2 pharmacokinetic studies of ethylmercury. The design and quality of the studies showed significant variation. The preponderance of epidemiologic evidence does not support an association between thimerosal-containing vaccines and ASD. Epidemiologic studies that support an association are of poor quality and cannot be interpreted. Pharmacokinetic studies suggest that the half-life of ethylmercury is significantly shorter when compared with methylmercury.**

Conclusions. **Studies do not demonstrate a link between thimerosal-containing vaccines and ASD, and the pharmacokinetics of ethylmercury make such an association less likely. Epidemiologic studies that support a link demonstrated significant design flaws that invalidate their conclusions. Evidence does not support a change in the standard of practice with regard to administration of thimerosal-containing vaccines in areas of the world where they are used.** *Pediatrics* **2004;114:793–804;** ***thimerosal, thiomersal, mercury, vaccine, methylmercury, ethylmercury, autism, autistic disorder, autistic spectrum disorder, developmental disorder, neurodevelopmental disorder.***

ABBREVIATIONS. ASD, autistic spectrum disorders; MMR, measles, mumps, rubella; EPA, Environmental Protection Agency; FDA, Food and Drug Administration; NDD, neurodevelopmental disorder; VAERS, Vaccine Adverse Events Reporting System; AE, adverse event; DTaP, diphtheria, tetanus, acellular pertussis; CI, confidence interval; CDC, Centers for Disease Control and Prevention; DTP, diphtheria, tetanus, whole-cell pertussis; HMO, health maintenance organization; RR, relative risk; ADD, attention-deficit disorder; GPRD, General Practice Research Database; DT, diphtheria, tetanus.

The prevalence of autism and autistic spectrum disorders (ASD) seems to be increasing,[1–9] through an actual increase in incidence, an increase in diagnosis as a result of improved detection through service agencies and schools, changes in case definitions, or changes in reimbursement for medical services and other care. Regardless of the reason, determining the cause of autism is critical to permit appropriate diagnostic, treatment, and preventive measures to be enacted. The major categories proposed as causing autism are genetic influence and prenatal or postnatal environmental factors.[10] Vaccines, particularly measles, mumps, and rubella (MMR) vaccine and thimerosal-containing vaccines, have been postulated as a cause for this increased prevalence of ASD.[11–16]

Mercury is known to be neurotoxic, and methylmercury poisoning clusters have been described as a result of environmental contamination. With ongoing industrial practices that create a global cycling of mercury, environmental exposures in food and from other sources is common, and in some areas ~8% of US women of childbearing age have levels above the Environmental Protection Agency (EPA) recommended reference level.[17,18] Consumption of contaminated foods is the main route of nonoccupational exposure; one 5.6-oz can of tuna on average contains 11.5 μg of Hg.[17] The reader is referred to several excellent reviews on the topic for more detailed information.[17,19–25] On the basis of data from areas of environmental contamination, in 1997, the EPA revised its mercury intake guidelines; it is now the most conservative guideline, and is one fourth the intake guidelines of the Food and Drug Administration (FDA). Five points about the EPA guideline

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should be noted: it is based on oral ingestion of methylmercury, not ethylmercury; it is meant as a starting point for investigation, not a level at which toxicity is thought to occur; it has a 10-fold safety factor built in; it was set to avoid toxicity to a fetus; and it assumes a cumulative dose if ingested daily over a prolonged period of time. All of these points are not directly relevant to thimerosal in vaccines, yet EPA guidelines have been applied to ethylmercury in thimerosal.

In 1998, the FDA reviewed thimerosal-containing products and found that >30 licensed vaccines contained thimerosal, which is ~50% ethylmercury, and that with the number of vaccines given in the first 6 months of life the 1997 EPA guideline could potentially be exceeded. The FDA subsequently requested that vaccine manufacturers remove thimerosal, where possible, from vaccines.[26] As of 2001, thimerosal in quantities sufficient to act as a preservative was removed from all vaccines in the childhood immunization schedule in the United States except some influenza vaccines.[27] Trace amounts of thimerosal, introduced during the manufacturing process to ensure sterility, are present in some vaccines, but the amounts are so small that exposure is inconsequential.

Although thimerosal as a preservative is no longer present in recommended vaccines for children younger than 7 years in the United States (except most influenza vaccines), thimerosal-containing vaccines continue to be used worldwide. In addition, practitioners are questioned regularly by parents about the possibility of an association and asked to provide their opinion on the safety of these vaccines. In 2001, the Immunization Safety Review Committee of the Institute of Medicine evaluated this issue and concluded that the evidence is insufficient to accept or reject a causal relationship between exposure to thimerosal and neurodevelopmental disorder (NDD).[28] Subsequently, several epidemiologic studies have been published[29–37] as well as studies evaluating the pharmacokinetics of ethylmercury.[38,39] In addition, the Institute of Medicine reconsidered the hypothesis that vaccines are associated causally with autism and rejected a causal relationship between MMR vaccine and autism and thimerosal-containing vaccines and autism.[40]

Evidence from randomized, controlled trials generally is considered the "gold standard" used to support medical decisions made by practitioners. However, in the context of an existing vaccination program, randomized, controlled trials are not possible. Therefore, the hypothesis of an association between thimerosal and autism has been tested in epidemiologic studies. Because epidemiologic studies are subject to many potential biases that may affect the validity of results, appropriate design and analytic methods are critical to achieve meaningful results. The purpose of this article was to identify systematically and evaluate critically the design, methods, analysis, and conclusions of each original research publication that has assessed the epidemiology of thimerosal and ASD. To address a potential biological mechanism for a link between thimerosal and ASD, we also critique published studies of the pharmacokinetics of ethylmercury in children.

METHODS

Search Strategy

To identify original research publications linking thimerosal-containing vaccines and autism or other neurologic conditions and original laboratory research on the human pharmacokinetics of ethylmercury in thimerosal, we searched the National Library of Medicine's Medline database using PubMed, and the Cochrane Library for articles published between 1966 and 2004. The terms thimerosal, thiomersal, vaccine, mercury, methylmercury, ethylmercury, autism, autistic disorder, autistic spectrum disorders, developmental disorder, and NDDs were selected as MeSH headings, and text words were combined in the search strategy. In addition, we used the "related links" option on PubMed. We also reviewed references in all relevant published articles, including reviews, letters, and commentaries, to identify original research.

Study Selection and Evaluation

Studies were assessed as to whether they should be included in this review on the basis of their reporting original data examining a possible link between thimerosal and ASD/NDDs or describing human pharmacokinetics of ethylmercury, which is found in thimerosal. Once a study met the inclusion criterion, data were extracted including first author, journal, year of publication, country of study, type of study, and database or laboratory data examined. Assessment of study methods included study design, type and size of population studied, definition of exposures and outcomes, validation of developmental diagnoses, provision of sample size calculations and/or discussion of study power, and statistical methods including techniques to control for potential confounding. We also determined whether the authors discussed potential limitations to the study. Assessments of all eligible studies were conducted independently, with differences resolved by all-author consensus. Study authors were not contacted for additional information because our goal was to evaluate data available in the original publications. Attempts were made to validate data used in the reviewed publications when the data sources were available publicly.

RESULTS

Of the abstracts of articles reviewed, 14 seemed to report original data. Two pharmacokinetic studies were excluded: one because it modeled theoretical estimates of mercury concentrations[41] and another because it used previously published data for half-life extrapolation of ethylmercury rather than reporting original data.[42] Characteristics of the remaining 12 studies are summarized in Tables 1 and 2. Ten studies are epidemiologic: 5 cohort studies investigating an association between thimerosal and autism/developmental disorders,[29,32–35] 3 ecological studies comparing trends in the incidence of autism with thimerosal exposure,[36,37,43] and 2 studies that present both retrospective cohort and ecological data.[30,31] Two of the purely ecological studies have overlapping data sets, and 1 of the retrospective cohort studies uses the same database as these 2.[33] One of the ecological studies[43] and 2 of the studies reporting cohort and ecological results[30,31] use the same data, some of which were used by the same authors in a third article, 1 of the retrospective cohort studies.[29] Two studies are pharmacokinetic studies of thimerosal in a cohort of human infants.[38,39] Both examine small numbers of patients without matched control subjects and thus are descriptive. Several quality measures were used to evaluate the cohort studies (Table 2). A summary of each article is pre-

TABLE 1. Characteristics of Epidemiologic Studies

Country, Year Published	Source	Analysis, Years of Study	Database
UK 2004	Andrews et al[34]	Retrospective cohort, 1988–1997	Office of National Statistics GPRD
UK 2004	Heron et al[35]	Prospective cohort, 1991–1992	ALSPAC; Child Health Surveillance
Denmark 2003	Hviid et al[33]	Retrospective cohort, 1990–1996	Danish National Registries
USA 2003	Verstraeten et al[32]	Retrospective cohort, 1991–2000	Three HMOs
USA 2003	Geier and Geier[29]	Retrospective cohort, 1992–2000	VAERS
USA 2003	Geier and Geier[30]	Retrospective cohort and ecological, 1992–2000	VAERS, US Department of Education Report
USA 2003	Geier and Geier[31]	Retrospective cohort and ecological, 1997–2000	VAERS, US Department of Education Report
USA 2004	Geier and Geier[43]	Ecological, 1981–1985, 1990–1996	US Department of Education Report
Sweden/Denmark 2003	Stehr-Green et al[36]	Ecological, Sweden 1987–1999, Denmark 1983–2000	National Inpatient Data (Sweden), National Registry (Denmark)
Denmark 2003	Madsen et al[37]	Ecological, 1971–2000	Danish National Registry

ALSPAC indicates Avon Longitudinal Study of Parents and Children.

sented, followed by a summary of principal methodologic concerns.

Cohort Studies

Of the 10 epidemiologic studies, 7 included cohort data (Table 1). Three of these articles reported an association between autism and thimerosal exposure. All 3 are by the same authors, and the data sets are overlapping.[29–31] The first of these to be published is a retrospective cohort study that used the Vaccine Adverse Events Reporting System (VAERS) database.[29] The authors analyzed information from the VAERS database on adverse events (AEs) reported after use of thimerosal-containing diphtheria, tetanus, acellular pertussis (DTaP) vaccines from 1992 to 2000 ($n = 6575$) and after use of thimerosal-free DTaP vaccines from a different time period, 1997–2000 ($n = 1516$). The authors then defined a cohort that included 88 children who were reported as having autism, mental retardation, or speech disorders. Of these children, 81 were in the thimerosal group (18 with autism) and 7 were in the thimerosal-free group (1 with autism). Gender, age, and onset in days after vaccination were extracted. Risk ratios were calculated on the basis of relative incidence of each diagnosis for the thimerosal-containing compared with the thimerosal-free group: autism, 6.0; mental retardation, 6.1; and speech disorders, 2.2. No confidence intervals (CIs) were provided. The authors concluded that there is a significant ($P < .002$ to $P < .05$) increase in these disorders after receipt of thimerosal-containing vaccines and that children who receive an additional 75 to 100 μg of thimerosal may have an associated increase in NDDs. Furthermore, the authors stated that reactions tended to occur in older children and speculated that this may be explained by the toxic buildup of mercury from successive doses of thimerosal-containing DTaP vaccines.

We identified multiple methodologic concerns regarding this article. The key outcome measure, calculation and comparison of AE incidence for thimerosal-exposed and unexposed infants, requires accurate and unbiased assessment of the numerator (children with defined AEs) and denominator (exposure/no exposure to thimerosal-containing DTaP) for the 2 groups. Several factors contribute to substantial inaccuracy in the numerator of AEs. VAERS is a passive reporting system that is monitored by the Centers for Disease Control and Prevention (CDC) and the FDA and to which anyone—health care provider, vaccinee, or parent—may report an AE after vaccination.[44] Although the authors postulated complete reporting of AEs by stating that "all adverse reactions are to be reported to the VAERS database as required by US law," in fact, reporting is mandated only for events included in the "injury table" of the National Vaccine Injury Compensation Program; ASDs and NDDs potentially associated with diphtheria, tetanus, whole-cell pertussis (DTP)/DTaP or thimerosal exposure are not mandated. Moreover, for these and other adverse reactions, substantial underreporting occurs.[44–46] Underreporting is particularly common for events that are not in the compensation program, for events that are not defined by a specific diagnostic test, or when the temporal relationship with vaccination is not well defined, both of which apply to the conditions evaluated in this study. In addition, events in VAERS are classified on the basis of a reported diagnosis or a coder's interpretation of symptoms/signs included in a comment field. Diagnoses are not validated. The authors do not report which diagnosis or symptom terms they abstracted from the VAERS database or how they dealt with diagnostic overlap or incomplete records. This is particularly troubling because the disorders reported have a long differential diagnosis and because the mean age reported for children with autism (1.7 ± 1.1 year) is below the age at which a reliable diagnosis of that disorder is made.[47,48] Demonstrating the statistical fragility of analysis of this database, if only 1 child who has autism and did not receive thimerosal-containing DTaP were misclassified into the thimerosal group or if 1 such child were not reported to the VAERS system, then the reported risk ratio would be reduced by half and the P value would be $>.05$.

In addition, several biases may have led to differential reporting of events in children who received DTaP vaccines that did or did not contain thimerosal as a preservative affecting the ability to compare relative reporting rates. In a setting of incomplete

TABLE 2. Evaluation Criteria of Cohort Studies

	Cohort Inclusion/ Exclusion Criteria Precisely Described	Outcome Measures (Diagnoses) Precisely Defined	Outcome Measures Validated for at Least a Sample or None of the Cohort	Methods to Calculate Risk Factor (Thimerosal) Exposure Described and Appropriate	Basis for Sample Size Described and/or Power Discussed	Study Controls for Bias and Confounding	Potential Impact of Bias on Results Discussed	Other Study Limitations Discussed
Andrews et al, 2004[34]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Heron et al, 2004[35]	Yes	No	No	Yes	No	Yes	Yes	Yes
Hviid et al, 2003[33]	Yes	Yes	No*	Yes	No	Yes	Yes	Yes
Verstraeten et al, 2003[32]	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Geier and Geier, 2003[29]	No	No	No	No	No	No	No	No
Geier and Geier, 2003[30]	No	No	No	No	No	No	No	No
Geier and Geier, 2003[31]	No	No	No	No	No	No	No	No

* Validity confirmed in a sample from the same database used for another study.

reporting, if parents or providers, either of whom can report to VAERS, are aware of a possible link between thimerosal exposure and NDDs, then reporting by either group may be greater among those who have been exposed ("reporting bias"). This bias also may have affected description of symptoms and had an impact on how events were coded. "Diagnostic bias," with providers more likely to diagnose autism or other NDDs among children who were exposed to thimerosal, also may have occurred. Because of FDA concern and subsequent recommendations by the American Academy of Pediatrics and the US Public Health Service for precautionary thimerosal removal in July 1999, with associated media interest, there was a substantial risk that these biases occurred in a study that includes AEs reported through 2000. VAERS data show markedly increased reporting of autism during the second half of 1999 and 2000, consistent with reporting bias.

An additional problem affecting numerator data is the inability to define accurately total thimerosal exposure in children with reported AEs VAERS reports include only the vaccine type and manufacturers for the visit associated with the AE and within 4 weeks before that date. It is not possible to define whether a child received thimerosal-containing or -free DTaP vaccine at previous visits or other vaccines that may or may not have included this preservative. As NDD risk was hypothesized by the authors to be related to the total thimerosal exposure rather than only thimerosal in DTaP, the inability to define that exposure represents a significant limitation.

Substantial questions regarding the accuracy of the denominator data for the incidence calculation also exist. The denominator requires the total number of children in the United States who received thimerosal-containing DTaP (exposed) and the total number who received thimerosal-free DTaP (unexposed). The authors indicated the source of these data as the "Biological Surveillance Summaries of the CDC." However, CDC reports only aggregate doses distributed for DTaP and other vaccines and provides no manufacturer-specific data.[49] It is unclear how the authors estimated manufacturer-specific data because, on the basis of agreements with manufacturers, CDC does not release these data. No source is cited in the publication. The authors provided no details on how total DTaP doses distributed were translated into number of children vaccinated with specific thimerosal-containing or thimerosal-free vaccines, which is particularly problematic for a vaccine administered in a 5-dose schedule over a 4- to 5-year period.

Two other publications by Geier and Geier reported essentially the same data with minor differences and thus are discussed together.[30,31] The articles have 3 components: first, data from the VAERS database again were presented but analyzed on the basis of different levels of thimerosal exposure (cohort data); second, a comparison between the FDA and EPA exposure limits was made with the dose received in routine vaccination; and third, the US Department of Education report on numbers of chil-

dren with neurologic disorders was compared with mercury exposure in vaccinations over time (ecological data). The ecological data are discussed in the section on ecological studies.

The cohort data in 1 article[31] evaluated reports of autism, personality disorders, and mental retardation for children who were exposed to thimerosal-containing and thimerosal-free DTaP vaccines using VAERS reports between 1997 and 2001, and the other[30] assessed autism, speech disorders, and heart arrest on the basis of VAERS reports of children who were exposed to thimerosal-containing DTP and DTaP vaccines from 1992 to 2000 compared with thimerosal-free DTaP vaccines from 1997 to 2000. DTaP vaccines were not licensed in the United States for use beginning at 2 months of age until 1996. The analytic strategy comparing incidence rates in these 2 articles is the same as in their first publication. However, the authors stated that in each of these analyses, they compared children who received an average of 37.5 μg of ethylmercury with children who received an average of 87.5 μg. The overall conclusion of both publications is that there is an association of heart arrest and neurologic disabilities with thimerosal.

As in the first Geier and Geier article, completeness in reporting, diagnostic specificity and validation, and potential diagnostic and reporting bias cannot be evaluated properly in these 2 studies,[30,31] particularly for the study that included data through 2001.[31] In addition, the authors did not present methods on how the ethylmercury exposure estimates of 37.5 μg and 87.5 μg were determined. Because VAERS reports do not include a child's entire immunization history and because vaccines that are reported to have been received before an AE are not verified by medical record review, estimated ethylmercury exposure from the reported vaccination visit may be inaccurate and total previous exposure would not be possible to estimate.

Four of the 7 cohort studies do not identify an association between thimerosal and ASD. One study is from the Vaccine Safety Data Link group from the CDC in the United States.[32] Data were collected from 3 health maintenance organization (HMO) databases on a total of 140 887 vaccinees. Data were screened for potential associations between NDDs and cumulative thimerosal exposure at 1, 3, and 7 months of age with exposure analyzed as both continuous and categorical variables. Relative risks (RRs) were calculated using a proportional hazards model. In the first phase of the study, data from 2 HMOs were analyzed. In the continuous variable analysis, an association at HMO A between thimerosal exposure at 3 months of age and tics was found (RR: 1.89; 95% CI: 1.05–3.38). At HMO B, cumulative exposure to thimerosal at 3 and 7 months of age was associated with language delay (3 months: RR: 1.13; 95% CI: 1.01–1.27, 7 months: RR 1.07; 95% CI: 1.01–1.13). In the categorical analysis, there was a negative association for speech delay with 87 to ≥175 μg Hg at 7 months in HMO A (87–162 μg: RR: 0.58; 95% CI: 0.37–0.93; ≥175 μg: RR: 0.58; 95% CI: 0.36–0.92). For HMO B, at 3 months of age, there was an association between ≥62.5 μg Hg and language delay (RR: 1.87; 95% CI: 1.08–3.23). Only HMO B included a sufficient sample size of patients with autism for analysis, and no association was found. An additional subanalysis was performed at HMO B, where children who were exposed to thimerosal-containing vaccines were compared with children who received only thimerosal-free vaccines; at 3 months of age, the only statistically significant association was a protective effect of thimerosal for attention deficit disorder (ADD; RR: 0.70; 95% CI: 0.52–0.95).

In the second phase, children in HMO C were assessed to evaluate further the associations seen in HMOs A and B, in an attempt to confirm the preliminary findings. There were no statistically significant associations. Because of limited numbers, RR at HMO C was calculated only for diagnoses of speech or language delay and ADD; no increased risk was found for either outcome. The authors concluded that no association can be confirmed or refuted between thimerosal and NDDs. The authors stated that because of the retrospective cohort study design and the need to resolve conflicting findings in the HMOs, additional studies need to be conducted.

This brief summary simplifies results of a complex analysis using a multifaceted data set. This cohort includes complete ascertainment of children with *International Classification of Diseases, Ninth Revision* coded diagnoses and complete vaccination histories, allowing accurate calculation of thimerosal exposure. Analytic methods are described clearly as are methods used to control for potential biases, such as differences in health care utilization. The authors found an association between thimerosal exposure and upper respiratory tract infection, suggesting that increased health care use may be a confounder, with children who have more visits receiving more vaccinations and being more likely to have a diagnosis of an NDD such as speech delay. To control for this, analyses for HMOs A and B were restricted to children who had made at least 1 visit to a clinic or an emergency department at the same age as cases. However, the authors did not document that this adequately controlled for differences related to health care use, and similar measures to control for potential confounding could not be implemented at HMO C.

The question of diagnostic accuracy was assessed for a subset of patients with an NDD by conducting chart review and documenting that the diagnosis was made by an appropriate specialist. Confirmation rates were variable, with a range from 28% for ADD to 92% for autism; rates varied by HMO. Interpreting associations for diagnoses with lower confirmation rates may be problematic.

Although this is the first peer-reviewed journal publication of these data, it is the third reanalysis of these data sets.[28,50] Each reanalysis has attempted to address methodologic problems, for example controlling for differences in health care–seeking behavior and analyzing data from HMOs A and B separately. Although these reanalyses may strengthen the overall analytic method, they create a risk of "investigator bias" whereby the investigators' beliefs re-

garding outcome could affect the analysis and results.

The fifth cohort study uses the Danish Civil Registration System to examine the rate ratio of ASD in children who received thimerosal-containing vaccinations to children who received thimerosal-free vaccinations.[33] In Denmark, the only thimerosal-containing vaccine given after 1970 was DTP; thimerosal was removed in 1992. Whole-cell pertussis vaccine continued to be administered until 1997, at which time Denmark changed to an acellular pertussis vaccine. Using the Danish Civil Registration System, Hviid et al[33] were able to connect registrants who were born between January 1, 1990, and December 31, 1996, to their vaccination records at the National Board of Health and their pertinent health records at the Danish Psychiatric Central Register, the National Hospital Discharge Register, and the Danish Medical Birth Registry. Medical histories of children were followed until pertinent diagnoses were made, children were lost from the system, or children reached 11 years of age.

On the basis of doses given at 5 weeks, 9 weeks, and 10 months of age, a child in Denmark before 1992 could receive a total of 125 μg of ethylmercury; after 1992, the exposure was 0. Incidence rates were analyzed with Poisson regression to calculate a rate ratio, per 25-μg ethylmercury increment, according to vaccination history. The rate ratio for autism for children who received any vaccinations that contained thimerosal (1 220 006 person-years) as compared with children who received only thimerosal-free vaccinations (1 660 159 person-years) is reported as 0.85 (95% CI: 0.06–1.20). For other ASDs, the rate ratio was 1.12 (95% CI: 0.88–1.43). When increments of 25, 75, and 125 μg Hg are compared, the rate ratios and CIs are similar. For assessing for possible misclassification of thimerosal-containing or thimerosal-free vaccine during the period of switchover (1992), data were reassessed excluding 1992, and results again were similar. For addressing possible confounders that might have changed in the population over time (eg, dietary mercury, ASD diagnostic criteria/incidence), the data were analyzed restricting the cohort to 1991–1993, and the results again were similar. Single imputation was used to evaluate the impact of missing values, and no impact was detected. The authors also evaluated the overall incidence of autism in Denmark during the study period and found a significant increase per calendar year (RR: 1.24; 95% CI: 1.17–1.31), even after discontinuation of thimerosal in vaccines. The authors concluded that although there is an increase in incidence of autism, there is no evidence of an association between thimerosal-containing vaccines and autism in the cohort that they studied and no indication of a dose-response association.

The organization of the Danish health system lends itself to the type of analysis presented in the article. The cohort includes complete ascertainment of children, developmental diagnoses, and immunizations. That all children in Denmark receive vaccines from a single manufacturer (the government) optimizes the ability to ascertain exposures accurately. Potential sources of error such as vaccinations received during the 1992 changeover period and changes in diagnosis of autism during the study period were anticipated and analyses were done to evaluate their possible impact. One weakness is that the validity of the ASD diagnoses was not ascertained because chart reviews were not performed. The authors dismissed this, citing a published paper using the same databases in which validity of ASD diagnosis was confirmed in 37 (92%) of 40 children.[51] On the basis of this information, it is unlikely to have significantly influenced the results for this diagnosis. Although the study population was large and included almost 3 million child-years of observation, no information is presented in the publication on the potential difference in the incidence in autism that the study is powered to detect. Moreover, the maximum thimerosal exposure in Denmark was 125 μg ethylmercury, which is less than what the potential maximum exposure would have been in the United States. However, thimerosal exposure started at an early age and would be important if sensitivity to thimerosal were age-related.

The sixth study in the cohort category was performed in the United Kingdom using the General Practice Research Database (GPRD).[34] In this retrospective cohort study, 100 572 term and 2471 preterm children who were born from 1988 to 1997 and had at least 2 years of follow-up were linked to their vaccination histories and codes for diagnoses of various NDDs. Data for an association between thimerosal and these disorders was evaluated using a Cox proportional hazards model. The thimerosal dose from DTP/diphtheria, tetanus (DT; the only thimerosal-containing vaccine in the United Kingdom in the routine childhood program) was calculated for each child using a calculation that reflected both the total dose and the age of vaccination such that comparisons could be made between children who received a higher dose of mercury earlier in life and children who received vaccination later in life and/or missed doses. In the term group, 96% of children eventually received all 3 doses of DTP/DT. However, there was sufficient variability in the timing of vaccination to enable comparison using this formula, which is well explained in the text of the article. The average length of follow-up was 4.7 years and ranged from 2 to 11 years. Overall, in the term group, 5831 (2.0%) neurodevelopmental diagnoses were made, 104 (0.1%) of these being autism and 70 (0.07%) being tics. Two-sided *P* values with hazards ratios and CIs were calculated for term and preterm infants separately, and the data also were analyzed after excluding all children who did not receive 3 doses of vaccine by age 366 days, to minimize potential bias related to exposure to medical care. The only diagnosis for which risk increased significantly with increasing thimerosal dose was tics (hazards ratio: 1.62; 95% CI: 1.05–2.50) for doses by 3 months. For general developmental disorder, unspecified developmental delay, and ADD, there was a protective effect associated with thimerosal exposure. Validation was performed by reviewing charts of primary care physicians for 152 children with neurologic diagnoses. The

dates of vaccination were found to be accurate, and in 122 (80%), it was confirmed that the child presented with the coded condition; in the other 30 (20%), there was no record of the diagnosis, it was coded incorrectly, or the diagnosis reflected parental concern only. In the 122 children with a confirmed diagnosis, 48 were transient problems and 31 were long term; specifically, 24 (89%) of 27 tics were reported as transient. The authors concluded that the borderline association found between thimerosal exposure and tics is likely to be a chance effect or the result of confounding and that there is no evidence of neurotoxicity in infants or children who are exposed to thimerosal in vaccines.

Similar to the VSD and Danish studies, the GPRD database includes longitudinal health care and immunization data on a large cohort of children.[34] Although of the 152 898 children in the database only 100 572 were included for analysis, the large majority of exclusions were because of missing birthdates, which would not be a source of bias. The remaining exclusions, of preterm infants and infants with prenatal or early postnatal conditions that would affect receipt of vaccination and NDD outcomes, are appropriate to avoid potential confounding. The methods, analytic approach, and statistical technique are described clearly and are appropriate. The high proportion of developmental diagnoses that were validated is reassuring, but the sample evaluated was small and validation rates are not presented by diagnosis. The authors discussed several potential impacts of confounding on study results. The apparent protective effect of vaccination for several NDDs may reflect an inability to exclude all children with underlying conditions that increase their risk of these outcomes and decrease their likelihood of timely vaccination. The authors also acknowledged an inability to control for socioeconomic status or to consider unrecorded medical conditions, although the possible impact of these factors is unclear. A potential limitation of all analyses that rely on diagnostic code data are the possible variability on how physicians record diagnoses and the potential impact of chief complaint on final diagnosis. However, this type of diagnostic bias could lead to spurious associations, rather than a lack of an association as found in this study. One limitation of this article is the lack of a discussion of the study power to detect significant associations for key NDDs, if such associations existed.

By contrast with the previous 3 studies, which analyzed diagnoses made by health care providers, the study by Heron et al[35] analyzed parental responses to questionnaires administered at 7 time points over 91 months. The Avon Longitudinal Study of Parents and Children in the United Kingdom evaluated development of children who were born in 1991 and 1992. Questionnaires included the Strengths and Difficulties Scales to define behavior ratings and the Denver II for fine motor development. Questionnaires also included screening questions for concerns about speech, tics, and special needs. Information on specific diagnoses, such as ASD, was not gathered but was expected to be reflected in the categories analyzed. Questionnaires also collected data on 9 potential confounders. Investigators were able to match 12 810 children who were evaluated in the Avon Longitudinal Study of Parents and Children study with their immunization histories in the UK Child Health Surveillance Database. Thimerosal dose was calculated as in the analysis of the GPRD database, taking into account both total dose and age at which the dose was given. Multivariate analyses, controlling for potential confounders, found negative associations for thimerosal exposure and conduct behavior, fine motor development, and tics. Only poor prosocial behavior at 47 months of age was significantly associated with thimerosal exposure at 3 months of age (odds ratio: 1.21; 95% CI: 1.01–1.23; $P = .031$). The authors concluded that the single association that they found may be expected given the 69 statistical tests performed and that early thimerosal exposure is not associated with a deleterious neurologic or psychological outcome.

Strengths of this study are that collecting data directly from parents avoids the potential confounding effects associated with health care utilization, and information could be collected on potential confounding variables such as socioeconomic status. There are a few concerns with this article, all of which are acknowledged by the authors. First, parental reports were not validated or compared with medical diagnosis. Second, developmental screens were problematic. Third, the questionnaire response rates varied from 65% for children with the maximum exposure to thimerosal to 48% for children with no exposure. The authors suggested that children with less thimerosal exposure also fall into a lower socioeconomic group and therefore have more risk factors for an adverse neurologic outcome, potentially creating a bias against finding an association. However, the potential impacts of response bias were minimized in the multivariate analysis, which controlled for socioeconomic status. Power was not addressed in this publication.

Ecological Studies

Five studies contain ecological data (Table 1). Two of these studies contain cohort data in addition to ecological data; the cohort data were reviewed above.[30,31] A separate ecological study by the same authors[43] reported essentially the same data as was presented in their cohort/ecological studies; thus, the ecological data of all 3 articles are discussed together. The authors compared the mean amount of ethylmercury in childhood vaccines with the number of cases of various disabilities reported in the US Department of Education system over time, using data from 1981 through 1985 and 1990 through 1996. To determine prevalence of disabilities, the US Department of Education report and the CDC's live birth surveillance data are analyzed.[52,53] Depending on the study, the conditions analyzed included autism, speech disorders, orthopedic impairments, visual impairments, and deaf-blindness. The authors then plotted the average thimerosal dose against the individual disabilities found and reported an association between speech disorders and autism with

thimerosal but no association with visual impairments, deaf-blindness, and orthopedic impairments. Odds ratios as compared with a baseline in 1984 and CIs >1 were reported. One of the studies also reported a correlation between the MMR vaccine and autism.[43]

There are several concerns with this analytic approach. The US Department of Education reports the number of people with each of the analyzed disabilities contained in their system, subdivided by age.[52] The authors determined prevalence by dividing these numbers by the number of live births recorded in the year in which that age group was born, as per the author reference to CDC data.[53] The accuracy of this approach depends on the assumption that the US Department of Education database is equally accurate and complete for each of the specified periods. If dropout was more common for the cohort born in 1984–1985 than that born in 1990–1994 and if reporting and diagnostic criteria differ during the time periods, then there may be spurious differences. Incidence of these disorders by birth cohort would provide a better measure of trends than does prevalence. To evaluate trends in exposure, the authors calculated the amount of ethylmercury administered on average to US children during the same time period. Although the ethylmercury dose did increase during the study period as a result of the widespread use of *Haemophilus influenzae* type b and hepatitis B vaccines, the methods did not consistently describe how ethylmercury exposure was calculated or which vaccines were evaluated. The authors stated that the ethylmercury dose "was based on the Biological Surveillance Summaries of the CDC," so the authors apparently divided the doses distributed by the birth year cohort to arrive at an average dose. Problems with this strategy include that the number of vaccines distributed in a certain year may not correspond with the number administered; and, again, the referenced report does not include manufacturer-specific data that would allow the investigators to separate thimerosal-containing from thimerosal-free vaccines distributed. In addition, the authors did not evaluate the vaccination histories of the children in the US Department of Education report; rather, they compared trends using 2 separate databases, thus the conclusion that the relationship between NDDs and ethylmercury is "linear," NDDs increasing with each microgram of mercury administered, is not valid. Although it is plausible that autism prevalence did increase at the same time that thimerosal exposure increased (with the introduction of new vaccines), a basic premise of epidemiology is that correlation does not make causation; this shortcoming and alternative hypotheses were not addressed.

The 2 other ecological studies reported data from Sweden and Denmark. The first article reported the incidence or case numbers of autism in Sweden and in Denmark from 1987 to 1999.[36] The authors then calculated cumulative ethylmercury exposure by multiplying the amount in vaccines used at the time by vaccination coverage rates (usually >95%) for each birth-year cohort and compared results with the incidence of autism. Both Sweden and Denmark discontinued thimerosal use during the study period, in 1992. The results for both countries were similar. Autism incidence or case numbers increased throughout the study period and continued to increase (although with some fluctuation) after elimination of thimerosal as a preservative in vaccines. The data are most compelling for Denmark, where autism prevalence rises substantially after thimerosal discontinuation. The authors concluded that their study constitutes compelling evidence against a thimerosal-autism correlation.

The design of this study is straightforward. The quality of records for autism diagnoses and vaccination rates and the size and stability of the population studied are strengths of this work. One concern is that incidence data were provided for Sweden but not for Denmark; however, these data were presented in a second publication, discussed below.[37] This study does have some limitations, which are discussed by the authors, and include the inability to control for or identify factors such as environmental exposure to methylmercury. Another limitation to all ecological data collected on this subject is that the criteria for the diagnosis of autism have changed and broadened over the years, making it difficult to interpret a reported increase in incidence or prevalence.

The last article in the ecological study category used the same data set but evaluated data from Denmark only.[37] This study expanded the Denmark information to include 1961–1970, when the cumulative ethylmercury dose was 200 μg in the first 15 months of life, and 1970–1992, when the dose was 125 μg in the first 10 months of life, as well as 1992–2000, when vaccines in Denmark did not contain thimerosal. The incidence of autism was stable until 1990 and thereafter increased throughout the study period, including the period when thimerosal was not included in vaccines. The authors concluded that there is no evidence for an association between thimerosal use in vaccines and autism.

The limitations of this study are similar to those discussed for the article by Stehr-Green et al.[36] In addition, because data were not available, outpatients with the diagnosis of ASD were not counted until 1995. This would increase the incidence rates for 1995 compared with previous years, as discussed by the authors. Rates continued to rise after 1995, however, when outpatients continue to be counted, so this is not likely to have affected overall conclusions of the analysis.

Laboratory Studies Describing Mercury Levels After Vaccination in Human Infants

Most studies of the pharmacokinetics and metabolism of organic mercury have evaluated methylmercury and have been performed with oral or inhalational absorption and are summarized elsewhere.[19,24] The first publication to describe ethylmercury (from thimerosal) pharmacokinetics in infants after injection was published by Stajich et al in 2000.[38] This study compared 20 infants in whom pre– and post–hepatitis B vaccination mercury levels were evaluated. Levels after vaccination were col-

lected at 48 to 72 hours. Fifteen infants who were born at <1000 g were compared with 5 infants who were born at >3500 g. Each dose of vaccine contained 12.5 μg of ethylmercury. The mean mercury level after vaccination was significantly higher ($P < .01$) in the preterm group compared with the term group (mean: 7.36 ± 4.99 μg/L vs 2.24 ± 0.58 μg/L, respectively). The mean value did not exceed the Department of Health and Human Services guidelines for "normal" blood mercury levels (<20 μg/L). On an individual basis, this value was exceeded in 1 preterm infant (range: 1.3–23.6 μg/L) but no infants in the term group (range: 1.4–2.9 μg/L). The authors raised concern for possible toxicity in the preterm population, although the significance of a 23.6-μg/L ethylmercury blood level in 1 infant is unknown. These data are useful in suggesting that the birth dose of hepatitis B vaccine does not substantially increase blood mercury levels in term infants and that levels are well below Department of Health and Human Services guidelines. It should be noted that the American Academy of Pediatrics and the Advisory Committee on Immunization Practices do not recommend hepatitis B vaccination in infants <1000 g unless the mother is HB surface antigen positive. For both the preterm and term groups, the small sample size limits the precision of the point estimates.

The publication by Pichichero et al[39] included data from 61 children: 40 recruited in Rochester, NY, who were exposed to thimerosal in vaccines compared with an unmatched control group of 21 children who were not exposed to ethylmercury in vaccinations recruited in Bethesda, MD. Although the Bethesda group is called a control, these children are not matched and the timing of blood mercury level testing is different. Children in the thimerosal-exposed group received up to 3 thimerosal preservative–containing vaccines (DTaP, hepatitis B, *Haemophilus influenzae* type b), and mercury levels were measured 3 to 28 days after vaccination. In the control group, samples were obtained at either the 2- or 6-month well-child visit. Urine and stool samples and maternal hair for total mercury content were studied for some infants, mostly in the thimerosal-exposed group. Results showed mercury concentrations below the limit of quantification in 12 of 33 infants in the study group and in 14 of 15 infants in the control group. Mean values were higher in younger patients, although exact means were not reported. The highest level reported was 20.6 nmol/L (parts per billion), which was less than the 29 nmol/L cited by the authors as thought to be safe in cord blood. Mercury also was found in stool specimens of infants who were exposed to thimerosal, suggesting excretion via the intestinal tract. The half-life of ethylmercury was calculated at 7 days (95% CI: 4–10 days), substantially less than the 20 to 70 days for methylmercury.

Although the absence of significantly elevated blood mercury levels in this study is reassuring, there are a number of limitations to the investigation. Most important, only 4 thimerosal-exposed children had blood specimens obtained within 5 days of vaccination—the period during which levels would be expected to be highest. In addition, baseline blood mercury levels were not obtained, so increases after exposure could not be characterized; and the exposed and comparison groups were not matched by age and were enrolled from different geographic areas. As the data showed higher mercury concentrations from maternal hair samples of the children who received thimerosal-containing vaccine, consistent with greater prenatal environmental exposure, the 2 groups are not the same at baseline and thus comparing them is problematic. Estimates of the half-life of ethylmercury were derived from a model and not from longitudinal observations of children. Although a difference between the half-lives of ethyl and methyl mercury is an important finding, directly assessing half-life would be more optimal than relying on modeled results.

Although not a pharmacokinetic evaluation, Geier and Geier[30,31] compared the FDA and EPA exposure limits with the thimerosal dose received in routine vaccination. They reported an "instantaneous excess" of mercury in vaccines on the basis of EPA and FDA standards of 3.2- to 32-fold. The data source and these calculations are understandable and reproducible. However, they are a misinterpretation of the EPA and FDA guidelines, which define their reference dose as "an estimate of daily exposure to the human population (including sensitive subpopulations) that is likely to be without a risk of adverse effects when experienced over a lifetime."[19] No standards exist for an "instantaneous," single-day dosage of ethylmercury delivered by intramuscular injection.

DISCUSSION

The quality and conclusions of 12 original studies on the potential association between thimerosal-containing vaccines and developmental disorders, including ASD, were examined in this review. Results of epidemiologic studies can contribute to assessment of causation but, by themselves, have several inherent limitations. Because they are observational rather than experimental, differences between study populations, multiple potential sources of bias, and the effects of confounding all can affect outcome. Thus, care in selecting the study group, defining and measuring exposures and outcomes, and analytic methods is crucial in obtaining meaningful results. Although consistency of results between multiple studies is 1 factor that can contribute to accepting or rejecting a causal relationship, a caveat is that only high-quality studies should be considered when evaluating consistency of findings. The 4 epidemiologic studies that support an association between thimerosal exposure and NDDs including autism, all by the same authors and using overlapping data sets, contain critical methodologic flaws that render the data and their interpretation noncontributory. The retrospective and prospective cohort studies that do not report an association, despite some limitations, generally were well designed and appropriately analyzed. Overall, these data support a conclusion of no association between thimerosal-containing vaccines and autism in children.

In a cohort study that finds no association, it is important to assess the study's power to detect a significant association, if it existed; none of the 4 quality cohort publications did so, although they did report CIs. Despite large numbers of children or child-years of observation included in the studies, because some of the measured outcomes were uncommon, power to detect significant associations may have been limited. One can assess the precision of a point estimate by CI width. For some analyses, the CI may include values that, taken individually, could seem clinically important; for example, a 95% CI from 0.78 to 1.71 represents a 5% chance that there is a 71% increase in the evaluated measure. Although this is not statistically significant ($P > .05$), some may believe that it is clinically significant. Conversely, when 4 quality studies do not consistently find statistically significant associations, an association that is found is most likely attributable to chance from multiple measures. In this context, although there may be a small chance that a clinically important association could not be detected by an individual study, the failure to detect an association in 4 well-designed cohort evaluations and 2 well-designed ecological studies supports that there truly is no association between thimerosal and ASD/NDDs.

A limitation in generalizing from the European studies to the United States is that total thimerosal exposure in the United Kingdom, Sweden, and Denmark were less than the potential maximum dose in the United States, and vaccination schedules differed; not including influenza, these amounts are 75 μg, 75 μg, 125 μg, and 237.5 μg of ethylmercury, respectively. However, a higher earlier exposure may be important if a true risk exists.

The pharmacokinetic studies, although limited by small sample sizes and differences in timing of specimen collection, suggest that blood mercury levels postvaccination in human infants are not in the range of known toxicity, making neurologic damage from thimerosal in vaccines unlikely. One caveat to this is that the blood level that could be associated with subtle neurotoxicity is controversial and thus makes pharmacokinetic studies difficult to interpret. The lowest Benchmark dose for a neurobehavioral endpoint after in utero exposure to methylmercury that the National Research Council considered reliable was 58 μg/L (parts per billion) in cord blood.[19,21] The postnatal threshold for subtle neurotoxicity is not known but likely would be greater than the lowest Benchmark dose for the more susceptible fetus. In any case, the highest levels found in these investigations are not in this range, although the timing of blood draws may not have been optimal. In addition, the results of the study by Pichichero et al,[39] demonstrating differences in the half-life and metabolism of ethylmercury and methylmercury, indicate that extrapolating experience with the latter to the former may be inappropriate.

Surprising, animal data on thimerosal pharmacokinetics are sparse. Magos[23,42] compared exposure to these 2 types of mercury in rats and found that methylmercury is actively transported across the blood-brain barrier, whereas ethylmercury is passively transported and is not as neurotoxic. An abstract published in 2003 on the pharmacokinetics in newborn monkeys also demonstrated a much shorter half-life for ethylmercury and lower brain levels.[54] Although there are anecdotal reports of mercury chelation aiding children with autism, there have been no controlled trials, and reports of mercury levels in autistic children are few. One study reported lower mercury levels in the hair of autistic children compared with control children; although the authors hypothesized that the mercury was absent from the hair because it was being retained in the brain, no evidence was presented to support this assumption.[55]

Ecological studies are subject to inherent limitations of this method. Changes over time in the diagnosis and reporting of autism and other NDDs make trends particularly difficult to evaluate. Nevertheless, data from Denmark and Sweden, where exposure to thimerosal in vaccines was eliminated in 1992 and where autism rates continued to increase, are consistent with the results of the quality cohort studies and the pharmacokinetic findings.

The evidence reviewed here indicates there is no association between thimerosal-containing vaccines and NDDs, including autism. Determining the cause of autism is important for future diagnosis, treatment, and prevention. However, as the evidence reviewed here suggests, these efforts may be substantially more productive if they are redirected to other hypotheses. Autism research dollars are limited, and parents of autistic children deserve to see finances directed to where they will do the most good. In addition, the evidence reviewed here does not support a change in the standard of practice with regard to administration of thimerosal-containing vaccines in areas of the world where their use is critical, such as economically developing countries. Removal of thimerosal as a preservative has resulted in the use of single-dose vials that are more expensive and increases the need for refrigerator space and other cold chain equipment. In much of the world, these constraints represent a substantial barrier and would result in far fewer children being vaccinated against serious and life-threatening vaccine-preventable diseases. It is well documented that unfounded concerns about vaccine safety can result in decreases in vaccination rates, subsequent disease outbreaks, and inefficient and ineffective utilization of scarce financial and research resources.[56,57] In the case of thimerosal and autism, a growing body of scientifically credible evidence suggests that there may be little to be gained from large additional research investments and, at a minimum, that it is time that additional significant investments in scientific or medical research related to thimerosal and autism be based on credible grounds that would lead one to believe that such investigations will contribute to understanding mechanisms that cause ASD.

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CERVICAL STITCHES ARE INEFFECTIVE

"A common surgical procedure long believed to help prevent premature births is ineffective, a new study has concluded. The study examined a technique called cervical cerclage, used in up to 2 percent of all pregnancies, according to Dr Kypros H. Nicolaides of the Kings College Medical School in London, an author of the study. The cervix is a sphincter of muscle that holds the fetus inside the uterus in pregnancy. Women whose cervixes have been damaged or are shorter than normal have long been thought to be at higher risk of premature deliveries. In cervical cerclage, stitches are inserted to shore up the cervix and give it added strength. The study, published on June 5 in *The Lancet*, involved more than 47 000 pregnant women in many countries. The women were examined with ultrasound. A group of 470 whose cervixes were short enough to put them at risk and who chose to participate were randomly assigned to get the procedure or not. Dr Nicolaides said the results confirmed that the length of the cervix accurately predicted preterm delivery. But the study also found that the cerclage procedure made no significant difference in the outcome; 22 percent of the women who had the surgery extended their pregnancy beyond 33 weeks, as did 26 percent of the control group."

O'Neil J. *New York Times.* June 8, 2004

Noted by JFL, MD

Health Journal / *By Tara Parker-Pope*

Controversial Study Reignites Debate Over Autism and Childhood Vaccines

JUST A FEW MONTHS after the nations' top medical adviser rejected a link between vaccines and autism, a mouse study has reignited the debate and raised new fears among parents considering vaccinations and flu shots for their kids.

For years, a cadre of parents and physicians have contended that thimerosal, an ethyl-mercury compound that has been one of the most widely used vaccine preservatives, is partly responsible for an apparent rise in autism in recent decades. But broad population studies haven't supported the claim. In May, a major report from the Institute of Medicine's Immunization Safety Review Committee, sought to put the debate to rest, rejecting a link between autism and vaccines.

But tomorrow, a congressional committee will review a June study from Columbia University, which found that a mercury preservative used in vaccines can indeed cause autism-like symptoms in a specific strain of mice. The research raises important questions about whether some people might be genetically vulnerable to the effects of thimerosal.

The study also raises questions about a new push by the Centers for Disease Control and Prevention to add flu shots to the immunization schedule for school-age kids. Thimerosal has been mostly phased out of childhood vaccines, which include shots for whooping cough and other illnesses. But the vast majority of flu shots given to both adults and children still contain the preservative. In addition, it's widely believed that many unexpired vials of thimerosal-containing childhood vaccines remain on the shelves of pediatricians' offices.

None of this is to say that parents should stop having their children vaccinated. Instead, critics of thimerosal say parents should insist on thimerosal-free vaccines and ask to check the label themselves before a child receives a shot.

Many researchers believe increased use of vaccines with thimerosal may help explain the alarming rise in autism in the U.S, which was just one in 2,500 children 20 years ago. Now CDC studies show the rate for autistic disorders in some areas to be as high as one in 150.

But the IOM report said an exhaustive review of the evidence doesn't support the claim that vaccines are to blame. The finding has sparked the ire of many autism researchers as well as parents who are convinced that vaccinations triggered autism in their kids. Among them is Congressman Dan Burton, an Indiana Republican, whose grandson developed autism five years ago after receiving shots containing thimerosal. Rep. Burton is chairman of the subcommittee that this week will hold hearings on the mouse study and other research. "We just need to get the mercury out of vaccinations," Rep. Burton says.

What is so frustrating to critics of the IOM report is that thimerosal is an entirely unnecessary ingredient. The mercury preservative typically is found in multidose vials to prevent contamination. But vaccines can be packaged in single doses and other preservatives can be used to protect multidose packs. Thimerosal remains in use in flu shots and adult vaccines mainly because of the cost of changing ingredients or switching to single-dose shots. "We have other ways to make vaccines safe," says Ellen Silbergeld, professor of environmental health sciences at Johns Hopkins Bloomberg School of Public Health.

The new mouse study bolsters the theory that genes involved in the immune system might make some people vulnerable to mercury—explaining why the vast majority of kids do fine after vaccines while a small number develop problems.

In the Columbia study, researchers administered thimerosal to four strains of young mice, injecting them with amounts comparable to those given to kids. Three of the mice strains were unaffected by thimerosal, but the fourth developed problems consistent with autism such as delayed growth, social withdrawal and brain abnormalities. The vulnerable mice were known to have a specific genetic susceptibility to mercury.

While a mouse study is far from conclusive, it's important to know that mice have long been a useful proxy for understanding human health. The researchers are close to developing a blood test to look for similar patterns in autistic children to see if the research translates to humans. Until more is known, says Mady Hornig, associate professor of epidemiology at Columbia's Mailman School of Public Health. "I think we should err on the side of caution and more thimerosal-free vaccine should be available."

Other experts say the mouse study offers little insight into the issue, but is needlessly upsetting parents and could undermine the nation's childhood vaccination program. Unproven worries about autism and vaccines are "hypothetical" compared to "a very real risk of disease," notes Marie McCormick, professor of maternal and child health at Harvard School of Public Health and chairwoman of the IOM committee.

Parents concerned that a pediatrician may have an old vial of thimerosal-containing vaccine can politely ask to see the label. Most doctors understand that parents can be nervous about vaccinations, says Ian Lipkin, director of the Center for Immunopathogenesis and Infectious Diseases at Columbia University and co-author of the mouse study. In addition, you can check Food and Drug Administration charts listing vaccines and their thimerosal status at www.fda.gov/cber/vaccine/thimerosal.htm.

Many doctors and clinics may not have a supply of thimerosal-free flu shots. Calling in advance may give a doctor enough time to obtain a single-dose syringe. Another option is to ask for Flu-Mist, a nasal mist vaccine that doesn't contain thimerosal.

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Journal Link: *Join a discussion with Health Journal columnist Tara Parker-Pope about the latest findings on autism, at* **WSJ.com/PersonalJournal**

Getting the Best Shot

Here are steps you can take to make sure your child receives a mercury-free vaccine.

Getty Images

- **Ask** for thimerosal-free vaccine
- **Check availability** before appointment
- Ask for vaccines in **single-dose** vials or syringes
- **Read** manufacturer label or insert to check ingredients yourself
- **Look up common vaccines** on www.fda.gov/cber/vaccine/thimerosal.htm
- Consider **intranasal flu vaccine** for school-age kids

A Case-Control Study of Mercury Burden in Children with Autistic Spectrum Disorders

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ABSTRACT

Large autism epidemics have recently been reported in the United States and the United Kingdom. Emerging epidemiologic evidence and biologic plausibility suggest an association between autistic spectrum disorders and mercury exposure.

This study compares mercury excretion after a three-day treatment with an oral chelating agent, meso-2,3-dimercaptosuccinic acid (DMSA), in children with autistic spectrum disorders and a matched control population. Overall, urinary mercury concentrations were significantly higher in 221 children with autistic spectrum disorders than in 18 normal controls (Relative Increase (RI)=3.15; $P < 0.0002$). Additionally, vaccinated cases showed a significantly higher urinary mercury concentration than did vaccinated controls (RI=5.94; $P < 0.005$). Similar urinary mercury concentrations were observed among matched vaccinated and unvaccinated controls, and no association was found between urinary cadmium or lead concentrations and autistic spectrum disorders.

The observed urinary concentrations of mercury could plausibly have resulted from thimerosal in childhood vaccines, although other environmental sources and thimerosal in $Rh_o(D)$ immune globulin administered to mothers may be contributory.

Regardless of the mechanism by which children with autistic spectrum disorders have high urinary mercury concentrations, the DMSA treatment described in this study might be useful to diagnose their present burden of mercury.

KEY WORDS: autism, autistic spectrum disorders, chelation, DMSA, mercury, thimerosal

Background

Recent studies have analyzed the prevalence of autism from the mid-1980s through 2002 in the United States and the United Kingdom.[1-5] The prevalence of autism is estimated to have risen from one in about 2,500 children in the mid-1980s to as common as one in 150 by 2002. Further, since all of these studies find the prevalence of autism in males to be four times that of females, the male prevalence of this disorder exceeds one in 100. These studies show that the rise in the prevalence in autism is genuine and not the result of population migration, differences in diagnostic criteria, or other potential confounders.

In 2001, the Institute of Medicine (IOM) of the United States National Academy of Sciences[6] determined that a link between mercury from thimerosal contained in childhood vaccines and the recent dramatic increase in neurodevelopment disorders is biologically plausible. Recent studies demonstrate a strong epidemiologic link between exposure to mercury from thimerosal contained in childhood vaccines and neurodevelopment disorders.[7-9]

The purpose of this study was to evaluate the concentration of mercury in the urine following a three-day treatment with an oral chelating agent, meso-2,3-dimercaptosuccinic acid (DMSA), in children with autistic spectrum disorders in comparison to a control population. Forman et al.[10] have reported on the use of oral treatment with DMSA in children exposed to metallic mercury. The authors found that oral chelation with DMSA produced a significant mercury diuresis in these children. They observed no adverse side effects of treatment. The authors concluded that DMSA appears to be an effective and safe chelating agent for treatment of pediatric overexposure to metallic mercury. In addition, extensive literature supports its safety in the chelation of lead from exposed children.

Methods

This study is a retrospective analysis of 221 consecutive children with previously established autism spectrum disorders referred and admitted to the International Child Development Resource Center (ICDRC). Each child had been diagnosed with autism (DSM-IV 299.00) or pervasive developmental disorder (DSM-IV 299.80) by outside physicians. A control population of 18 children was also identified without autism spectrum disorders in themselves or among their siblings or their first-degree family members. These healthy children presented to the ICDRC for elective determination of their levels of environmental mercury exposure at the request of their families, and are included here for case comparison. The Arizona State University Institutional Review Board approved our retrospective examination of cases and controls in this study.

All children were examined to exclude those who had dental amalgams. Among the 221 cases, all had received their full scheduled childhood immunizations appropriate for their respective ages. Among the 18 controls, 10 children had received their full childhood immunization schedules, and 8 children had received no childhood immunizations because of religious objections.

Informed consent was obtained from both cases and controls for DMSA chelation treatment. Controls and cases were both challenged with a three-day oral treatment of DMSA (10 mg/kg per dose given three times daily). After the ninth dose, the first voided morning urine was collected (when possible), or an overnight urine collection bag was worn. All laboratory analyses were performed by the Doctors' Data, Inc., in Chicago, Ill. The response to DMSA was measured as micrograms of mercury per gram of creatinine using inductively coupled mass spectrometry, and creatinine was measured using the Jaffe method. The laboratory was not informed whether the specimens were from cases or controls.

In addition to the overall excretion data, several epidemiologic case-control studies were conducted using the available populations. First, it was possible to match 88 cases against 16 controls for age (within one year) and sex, and overall post-DMSA urinary

mercury concentrations were determined. Second, it was possible to match 55 cases against 8 vaccinated controls for age, sex, and vaccine status, and overall post-DMSA urinary mercury, cadmium, and lead concentrations were determined. Finally, as epidemiologic controls, it was possible to match 5 each of vaccinated and unvaccinated controls for age and sex, and overall post-DMSA urinary mercury, cadmium, and lead concentrations were determined.

The statistical package contained in Excel® and SISA[7] was employed in this study. We determined means, relative increase (RI) in mean heavy metal excretion in cases compared with controls ($mean_{cases}/mean_{controls}$), standard deviation, and statistical significance using a t-test. Our null hypothesis was that the populations under study should have similar distributions of excreted heavy metals, and we accepted a double-sided P-value of <0.05 as statistically significant.

Population Type	Number of Boys	Number of Girls	Mean Age in Years (Range)	Mean Urinary Mercury (mcg/ g) creatinine (Range)
Cases	183	38	6.25 (3 to 15)	4.06 ± 8.59 (0 to 58.65)
Controls	14	4	8.85 (3 to 16)	1.29 ± 1.54 (0 to 6.2)

Table 1. Summary of 221 Cases and 18 Controls

Results

Table 1 summarizes the number of males and females, mean age in years, and average mcg Hg/g creatinine after DMSA treatment among our 221 cases and 18 controls. Among our 221 cases the boy:girl ratio was 4.88:1, and among our 18 controls the boy:girl ratio was 4:1. Urinary mercury concentrations were significantly higher in cases than in controls (RI=3.15; P < 0.0002; 95% CI: 1.43 to 4.11).

In the first part of our case-control analysis, we determined the mean and standard deviation of the concentrations of urinary mercury in the 88 cases (5.45 ± 10.9 mcg Hg/g creatinine) and 16 age and sex-matched controls (1.45 ± 1.57 mcg Hg/g creatinine) after DMSA treatment. The urinary mercury concentrations were significantly higher in cases than in controls (RI=3.76; P < 0.002; 95% CI: 1.60 to 6.41).

The results of the second part of our case-control analyses are summarized in Table 2. We determined the mean and standard deviation of the urinary mercury concentrations in the 55 cases (6.42 ± 12.69 mcg Hg/g creatinine) and 8 age, sex, and vaccine-status-matched controls (1.08 ± 1.12 mcg Hg/g creatinine). We determined that cases had a significantly higher urinary concentrations of mercury after DMSA treatment than did controls (RI=5.94; P < 0.005; 95% CI: 1.90 to 8.79). As shown in Table 2, both groups had similar urinary concentrations of cadmium and lead after DMSA treatment. Among our age and sex-matched healthy children, we determined that 5 vaccinated controls had similar urinary concentrations of mercury, cadmium, and lead after DMSA treatment compared with 5 unvaccinated controls, as is summarized in Table 3.

	Heavy Metal Examined	Population Examined	Heavy Metal Level (mcg/g creatinine)
	Mercury	55 Cases	6.42 ± 12.69
	Mercury	8 Controls	1.08 ± 1.12
Statistical Assessment			Relative Increase = 5.9 P < 0.005 95% CI: 1.90 to 8.79
	Cadmium	55 Cases	0.48 ± 0.42
	Cadmium	8 Controls	0.36 ± 0.22
Statistical Assessment			Relative Increase = 1.3 P = 0.35 Not Significant
	Lead	55 Cases	18.2 ± 43.3
	Lead	8 Controls	11.8 ± 8.6
Statistical Assessment			Relative Increase = 1.5 P = 0.34 Not Significant

Table 2. Matched Cases and Controls for Heavy Metal Levels Following a 3-Day DMSA Treatment

	Heavy Metal Examined	Population Examined	Heavy Metal Level (mcg/g creatinine)
	Mercury	5 Vaccinated Controls	0.70 ± 0.71
	Mercury	5 Unvaccinated Controls	1.98 ± 2.40
Statistical Assessment			P = 0.35 Not Significant
	Cadmium	5 Vaccinated Controls	0.42 ± 0.27
	Cadmium	5 Unvaccinated Controls	0.50 ± 0.27
Statistical Assessment			P = 0.65 Not Significant
	Lead	5 Vaccinated Controls	14.0 ± 10.1
	Lead	5 Unvaccinated Controls	16.1 ± 8.5
Statistical Assessment			P = 0.73 Not Significant

Table 3. A summary of a comparison of matched vaccinated and unvaccinated controls for heavy metal levels following a three-day DMSA treatment

Discussion

This study shows a strong association between increased urinary mercury concentrations following three days of treatment with DMSA and the presence of an autistic spectrum disorder. The statistically significant association persists when vaccinated cases are compared with matched vaccinated controls. No association was found between post-DMSA urinary cadmium or lead concentrations and autistic spectrum disorders. Lastly, although the study populations were small, the heavy-metal concentrations measured in matched vaccinated and unvaccinated control children were small and showed no statistically significant differences in urinary mercury, cadmium, and lead concentrations following a three-day treatment with DMSA.

Previously, Stajich et al.[11] showed that newborn infants had significant ($P < 0.01$) several-fold increases in the blood concentrations of mercury during the 48 to 72-hour period following immunization with thimerosal-containing childhood vaccines, compared with pre-vaccination levels.

Pichichero et al.[12] examined the concentrations of mercury in the blood, urine, and stool 3 to 28 days following thimerosal-containing vaccines in 40 full-term infants of age 6 months and younger in comparison to 21 control infants receiving thimerosal-free vaccines. The mean mercury doses received by thimerosal-exposed subjects were 45.6 mcg (range 37.5-62.5) for 2-month-old infants and 111.3 mcg (range 87.5-175.0) for 6-month-old infants. Blood mercury concentrations in thimerosal-exposed 2-month-old infants ranged from less than 3.75 to 20.55 nmol/L; in 6-month-old infants, all values were lower than 7.50 nmol/L. Only 15 blood samples from controls contained quantifiable mercury.

Concentrations of mercury were low in the urine after vaccination but were high in the stools of thimerosal-exposed 2-month-old infants (mean 82 ng/g dry weight) and 6-month-old infants (mean 58 ng/g dry weight) The authors estimated that the blood half-life of ethylmercury was 7 days (95% CI 4-10 days). The study was unable to determine the ultimate disposition of most of the mercury with which infants were injected.

Our analysis shows that children who developed autistic spectrum disorders had significantly greater accumulated mercury than controls. Our results are similar to those of the retrospective study by Holmes et al.[13] They observed that there was a significant relationship between increasingly severe autism and decreasing mercury levels in first baby haircuts in comparison to normal controls. Our results and those of Holmes et al. probably result from a decreased ability of children with autistic spectrum disorders to excrete mercury, resulting in the retention of potentially toxic mercury levels.

Impaired sulphation is observed in autistic spectrum disorders, and this biochemical deficit, possibly a pre-existing genetic condition, may contribute to the observed mercury accumulation, since the normal mechanism of clearing mercury from the body is thought to involve the binding of mercury compounds to sulfhydryl groups.[14]

Mercury concentrations in the human brain are six times greater than the blood.[15] This stems from the fact that thimerosal contains the ethylmercury radical attached to the sulfur atom of the thiol group of salicylic acid Generally, mercuric ions bind tightly but reversibly to thiol ligands.[16] It is likely, therefore, that the ethylmercury cation of thimerosal dissociates from the thiosalicylic acid moiety immediately after injection to bind to the surrounding thiol ligands present in great excess in tissue proteins.[17]

The buildup of mercury in the tissues of children is particularly alarming in light of a recent article by Baskin et al.[18] They have examined the toxic effects of micromolar concentrations of thimerosal in cultured human cerebral cortical neurons and in normal human fibroblasts. The results demonstrated that thimerosal in micromolar concentrations induced membrane and DNA damage, and initiated caspase-3 dependent apoptosis in human neurons and fibroblasts. In addition, the authors report that thimerosal toxicity may occur at even lower doses than those utilized in their experiments with longer times of exposure. Another recent study by Makani et al.[19] has also demonstrated high cellular toxicity of thimerosal in low micromolar concentrations in T-cells incubated with thimerosal for 24 hours.

A recent article by Nelson and Bauman[20] stated that the overall clinical picture of mercurism–from any known form, dose, duration, or age of exposure–does not mimic that of autism and that no evidence has yet been brought forward to indicate that children exposed to vaccines containing mercurials have more autism than children with less or no such exposure. However, the National Toxicology Program (NTP) within the U.S. Department of Health and Human Services, an interagency program headquartered at the National Institutes of Health's National Institute of Environmental Health Sciences (NIEHS), reports that clumsiness, speech impairment, and emotional disturbances are commonly observed with both acute and chronic thimerosal exposure. These mercurial symptoms are core to the observed abnormalities in autistic spectrum disorders. This observation is supported by Green et al.,[21] who recently reported that clumsiness is a commonly observed comorbidity in Asperger's Syndrome, an autistic spectrum disorder.

The results of our present study, combined with the published observations included above, disagree with the views expressed by Nelson and Bauman and support the hypothesis of Bernard et al.,[22] who have compared the similar biological abnormalities commonly found in autism and the corresponding pathologies arising from mercury exposure. Distinct similarities were found between autism and mercury exposure in their effects upon biochemistry, the immune system, the central nervous system structure, neurochemistry, and neurophysiology.

Another study by Bernard et al.[23] has further examined the relationship between thimerosal and autism. They determined that thimerosal was first added to childhood vaccines in the 1930s, and autism was first described in 1943 among children born in the 1930s, suggesting that autism may indeed be an iatrogenic effect of thimerosal.

In addition, Redwood et al.[24] have reported that mercury exposure from childhood immunization is a cause for concern because exposure to low levels of mercury during critical stages of development has been associated with neurological disorders in children, including attention deficit disorder (ADD), learning difficulties, and speech delays.

Moreover, our findings appear to confirm previously published epidemiologic evidence showing a direct association between increasing mercury from thimerosal-containing childhood vaccines and neurodevelopment disorders in children.[3-9] These studies showed that there was a two to sixfold, statistically significant increased incidence of neurodevelopment disorders following an additional 75-100 mcg dosage of mercury from thimerosal-containing childhood vaccines in comparison to thimerosal-free childhood vaccines. These studies showed dose-response curves demonstrating a close, statistically significant correlation between increasing mercury doses from childhood vaccines and childhood neurodevelopment disorders.

The results of our analyses suggest that mercury should be removed immediately from all biologic products, and others have reached a similar conclusion. Kravchenko et al.[25] stated, "Thus thimerosal, commonly used as a preservative, has been found not only to render its primary toxic effect, but also [to be] capable of changing the properties of cells. This fact suggests that the use of thimerosal for the preservation of medical biological preparations, especially those intended for children, is inadmissible." Cox and Forsyth[26] reported, "However, individual cases of severe reactions to thimerosal demonstrate a need for vaccines with an alternative preservative." Similarly, "...reactions can be expected in such a high percentage of merthiolate-sensitive persons that merthiolate in vaccines should be replaced by another antibacterial agent."[27] Rohyans et al.[28] revealed in 1984, "Although aqueous merthiolate has been used for years as a topical antiseptic, a recent review of its use by the Food and Drug Administration resulted in its classification as 'less than effective.' Furthermore, two of the ingredients (thimerosal and borate) in merthiolate are toxic if absorbed or injected." In addition, Seal et al.[29] reported in *The Lancet*, "Thimerosal is a weak antibacterial agent that is rapidly broken down to products, including ethylmercury residues, which are neurotoxic. Its role as a preservative in vaccines has been questioned, and the pharmaceutical industry itself considers its use as historical."

Conclusion

Analysis of post-DMSA urinary mercury excretion found a strong, statistically significant association between greatly increased urinary mercury concentrations and the presence of autistic spectrum disorders in vaccinated children.

The mercury levels measured in this study could plausibly have resulted from exposure to mercury in routine childhood vaccines in the United States, while thimerosal in $Rh_o(D)$ immune globulin and other potential environmental sources of mercury may be contributory.

Our study is unable to determine whether the statistically significantly higher urinary concentrations of mercury measured in cases in comparison to controls is caused by higher exposure to mercury, reduced ability to excrete mercury, or a combination of these explanations. Regardless of the mechanism by which children with autistic spectrum disorders accumulate high mercury levels, the DMSA treatment course described in this study appears useful and important in determining mercury body burden.

The data from this study, along with emerging epidemiologic data showing a link between increasing mercury doses from childhood vaccines and childhood neurodevelopment disorders, increases the likelihood that mercury is one of the main factors leading to the large increase in the rate of autism and other neurodevelopment disorders. It is to be hoped that removing thimerosal from all childhood vaccines will contribute to a decline in the numbers of new cases of autistic spectrum disorders.

Unfortunately, as discussed in a recent publication,[39] many of the vaccines recommended for the childhood immunization schedule contained the full doses of thimerosal through 2002 (FDA, personal communication), and in addition, pediatric vaccines such as influenza, diphtheria-tetanus (DT), and possibly others, still contain the full amounts of thimerosal in 2003. Therefore, it may be quite some time before a decrease in the prevalence of neurodevelopment disorders is seen.

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Potential conflict of interest: Dr Mark Geier has been an expert witness and a consultant in cases involving adverse reactions to vaccines before the U.S. Vaccine Compensation Act and in civil litigation. David Geier has been a consultant in cases involving adverse reactions to vaccines before the U.S. Vaccine Compensation Act and in civil litigation.

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Sensible Action For Ending Mercury-Induced Neurological Disorders

A Brief Analysis of Recent Efforts in Medical Mercury Induced Neurological and Autism Spectrum Disorders

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Executive Summary

In the subsequent five years since the joint US Public Health Service and American Academy of Pediatrics statement of 1999 alerting the public and practitioners to the potential harms of mercury in medicine, specifically Thimerosal (a mercury-laden preservative used in numerous vaccines), there has been a great body of work investigating the link between Thimerosal and neurodevelopmental disorders (NDD) including, and especially, autism.

Within their joint statement, the USPHS and the AAP offered the following:

> *"...because any potential risk is of concern, the Public Health Service (PHS), the American Academy of Pediatrics (AAP), and vaccine manufacturers agree that thimerosal-containing vaccines should be removed as soon as possible. Similar conclusions were reached this year in a meeting attended by European regulatory agencies, European vaccine manufacturers, and FDA, which examined the use of thimerosal-containing vaccines produced or sold in European countries."(Thimerosal in Vaccines: A Joint Statement of the American Academy of Pediatrics and the Public Health Service, July 09, 1999)*

These matters did not come to the forefront of scientific or public discourse due to any inherent danger by a specific vaccine, but rather the previously overlooked potential cumulative effect of multiple vaccines being given over a short schedule in our nation's continuing attempt to ward off epidemic and pandemic disease.

In 2001, the Institute of Medicine (IOM) published their first report in what would become a multi-year investigation, including several interim public meetings for the presentations of the most up to date scientific finds. In that report, *Immunization Safety Review: Thimerosal - Containing Vaccines and Neurodevelopmental Disorders (2001)*, the IOM would lay out a well crafted and accepted plan for those necessary scientific efforts to formidably bring answers to the issue. The IOM advised the relevant US government agencies (HHS, PHS, FDA, CDC, NIP) and independent researchers that a combination of epidemiological, animal model, clinical and case studies would be required by the tenets of good science to adequately review and make sound and well-founded determination regarding a possible vaccine-NDD/autism link.

Also in 2001, SafeMinds would learn through Freedom of Information Act (FOIA) requests that the National Immunization Program and Centers for Disease Control and Prevention had already conducted a review within the Vaccine Safety Datalink (VSD) to see if there was any epidemiological link between vaccines and NDDs including autism. That initial effort, led by then CDC research fellow Dr. Thomas Verstraeten, would not be offered to the public or the IOM for review. Verstraeten's findings showed a strong relationship between enhanced vaccination schedules and numerous symptoms of neurodevelopmental disorders including autism. As will be discussed later, it will not be until a much revised, redacted and watered down version could be accomplished that the CDC would allow the publishing of Verstraeten's work. While no additional scientific or evidentiary review will be accomplished in the interval

between Verstraeten's initial and final reports, the conclusions would change to reflect a lack of evidence supporting a vaccine-NDD/autism link.

From 2001 through the IOM-Immunization Safety Review Committee's (ISRC) May 2004 final report and disbanding, it would become apparent that a sole focus upon epidemiological studies in the US and various European countries would be the CDC/NIP's singular response to the vaccine-NDD/autism hypothesis. Nearly all of these studies, either CDC/NIP sponsored or selected through an exclusive network of conflicted researchers, were found to have been rife with major flaws in methodology and failing to follow acceptable standards in epidemiological practice.

Countering the CDC/NIP response are numerous independent research efforts supported through a mix of academic, private and non-profit foundational, and individual resources. Nearly 100% of non-conflicted research filling the gaps originally called for by the IOM (epidemiology, animal model, clinical, toxicology, case and genomic studies) has shown not only support to the vaccine-NDD/autism hypothesis, but also the elemental furthering in understanding to the biophysical path between exposure and injury.

As early as 1977, Russian researchers began recognizing the potential health hazards from ethyl mercury exposures. Additional studies conducted through the 1980s also documented toxic results from the utilization of thimerosal in various preparations and vaccines.

First afforded in *Autism: a novel form of mercury poisoning (2000)*, Bernard et al laid out the hypothesis of causality between Thimerosal and NDD/autism and the mimicking properties between autism and mercury poisoning. Verstraeten's original findings proved clearly the epidemiological support to the Thimerosal-NDD/autism, but even those have been buttressed by original and review efforts by others including Blaxill.

Boyd Haley, PhD, professor and chair at the University of Kentucky, Department of Chemistry and H. Vasken Aposhian, Ph.D., Professor, Molecular and Cellular Biology, University of Arizona have both clearly offered to the discussion, and revealed to the IOM/HHS communities, the well founded biological harms seen from ethylmercury (Thimerosal), especially upon the developing fetal/infant/toddler brain. In addition, these researchers have shown the biological variables (age, sex, and synergistic toxicities) that come into play regarding mercury exposure and subsequent injury. Aposhian also went further and offered that the inability for a select population to have an inhibited ability to naturally excrete the heavy metal mercury (as a larger population appears to have the capacity for) is not new to science. In fact, such a syndrome would mimic another well-recognized process called Wilson's Disease, where a problem excreting the heavy metal copper creates a similar, though not exact, set of circumstances and symptoms.

Issues regarding changes in diagnostics have also been offered as a potential reason for the increases in the autism population's relationship to increased immunizations. While a few efforts were offered to support that hypothesis, all have subsequently been disproved through review of the data, or independent analysis. The suggested benchmark for such data, California's Department of Developmental Services, dispels this theory. While admitting minor

changes may be inferred by changes in diagnostic criteria, reviewers of the data are comfortable that the exponential increases in autism cannot be supported through minor diagnostic coding changes, and to suggest so is not a defensible position.

In 2003, *A Case-Control Study of Mercury Burden in Children with Autistic Spectrum Disorders* was published by Jeff Bradstreet, MD, FAAFP, which clinically supported Aposhian's position of the inability of a select population to efficiently excrete mercury. This research provided that it was possible for a child to have a bioaccumulation of mercury from multiple vaccinations that would lead to eventual neurotoxicity and injury. Bradstreet went forward into a genomic survey of affected and non-affected children, and found specific abnormalities (or single recognized nucleotide polymorphism) found in children with autism spectrum disorders providing actual mapping from exposure to injury.

Dr. Andrew Wakefield and Dr. Jill James joined Bradstreet in presenting *Biological Evidence of Significant Vaccine Related Side-effects Resulting in Neurodevelopmental Disorders.*

Further evidence is provided by:

- Richard C. Deth, PhD (Northeastern University, Boston, MA) et al providing scientific understanding of mercury/thimerosal potential influence in pre- and post-natal development
- Burbacher et al, under NIAID/NIH/HHS funding, provided in primate models what had long been disputed: the ability for ethylmercury to cross the blood/brain barrier and be allowed to accumulate to toxic levels. (Requests for HHS to fund necessary further research to qualify the results have gone unanswered.)
- Dr. Mady Hornig (Mailman Schoold of Public Health, Columbia University) et al, looked at the effects of vaccine level thimerosal exposure on mice with a specific genetic susceptibility. Hornig found that the selected mice universally showed an implication of "genetic influences" that led to responses and activities that mimic those found in Autism Spectrum Disorders.

In short, while one side relies singularly and consistently upon proved flawed population-based epidemiology, or sequestered research findings, independent research filling much of the requirements of good science, and the IOM's stated needs, has amassed an appreciable body of evidence that, at minimum, proves the need for funding appropriate and independent research to follow through until all of the answers are found. In following another tenet of good science, while the independent (non-governmental, government sponsored or otherwise conflicted) have always readily made their efforts and data transparent and open for review. To re-secure the public's trust in our nation's immunization program, and affiliated research, every effort should be expended to assure that such openness and transparency is shared by all involved in the discourse.

Introduction

The Coalition for SafeMinds (Sensible Action For Ending Mercury-Induced Neurological Disorders) is a private nonprofit organization founded to investigate and raise awareness of the risks to infants and children of exposure to mercury from medical products, including thimerosal in vaccines. SafeMinds supports research on the potential harmful effects of mercury and thimerosal.

Our mission is to end the health and personal devastations caused by the needless use of mercury in medicines. Utilizing a multifaceted approach, we: (1) work aggressively with government agencies, legislators, manufacturers, and retailers to ensure the removal of mercury from medical and health-related products; (2) press for more research to understand scientifically how mercury in these products causes harm and how effective treatments can be developed for those already exposed; (3) create awareness campaigns to educate parents, clinicians and policy makers about the issue; and (4) encourage open investigations into how mercury has persisted in routine medical products like vaccines despite its known neurotoxicity. To accomplish these goals, we serve actively in the scientific, legal, regulatory, legislative, and public awareness arenas.

SafeMinds believes it is important to acknowledge our belief that vaccines are an integral part of our public health infrastructure, and their importance to that system cannot be understated. That said; we also feel strongly there is an inherent integrity necessary for the continued safety and success of US vaccination efforts. It is to this integrity through safety issue that SafeMinds is looking to support and bolster immunization policies and programs. It will only be through the restoration of the public trust that the successes of past vaccine campaigns can be realized in the future. SafeMinds also firmly believes that parents should be fully informed of the benefits and risks associated with mandatory vaccinations, and that medical, religious, and philosophical exemptions to immunizations should be preserved. States that do not have all three exemptions should review their policies and consider at a minimum to have viable medical and religious exemptions instituted.

A Brief Recap of Autism: A Novel Form of Mercury Poisoning

In 2000, SafeMinds founders presented and published a research effort that aided in propelling this issue into the awareness of the public and government officials. That endeavour, *Autism: A Novel Form of Mercury Poisoning*[1] (Bernard, Enayati, Redwood, Roger, Binstock) was and remains recognized as a cornerstone document to the discourse on medical mercury exposure and toxicity and its effects on health. In the study, Bernard et al compiled bodies of data, including that of various US government agencies, from several facets of the issue and mapped the path between thimerosal (a widely utilized mercury laden preservative often found in vaccines) and neurological development disorders, including autism.

Autistic spectrum disorder (ASD) is a neurodevelopmental syndrome with onset typically prior to age 36 months. Diagnostic criteria consist of impairments in sociality and communication plus

[1] Bernard et al, *Autism: a novel form of mercury poisoning*, Medical Hypotheses (2001) 56(4), 462–471

repetitive and stereotypic behaviors and stereotypic behaviors. Traits strongly associated with autism include movement disorders and sensory dysfunctions. Although autism may be apparent soon after birth, most autistic children today experience at least several months, even a year or more of normal development – followed by regression, defined as loss of function or failure to progress.[2]

In the 2000 report, SafeMinds recounted the history of events illuminating the neurotoxicity of mercury (Hg):

- Mercury-contaminated fish in Japan - Minimata Disease
- Mercury-tainted grain in Iraq, Guatemala and Russia
- Acrodynia also called Pink Disease induced by mercury in teething powders
- Numerous instances of mercury poisoning through occupational exposures – Mad Hatter's disease
- Numerous animal and in vitro studies providing insights into the mechanisms of mercury toxicity

Based on the admission by the US Food and Drug Administration (FDA) that thimerosal, a product that had been banned as an Over-the-Counter product, was still in use as a vaccine preservative; and that infants were exposed to levels of mercury in excess of federal safety guidelines, SafeMinds looked at the possible consequences to this exposure. This announcement coupled with a significant number of parents reporting the onset of symptoms shortly after immunization and the direct correlation in the increased prevalence of ASD and the increased exposure to infants to thimerosal through immunizations, highlighted the need to review the science in both areas to determine if acquired autism was a novel form of mercury poisoning. (Acquired autism is also sometimes called regressive autism. It is this form of autism that has become more prevalent in the last 15 years.)

ASD manifests a constellation of symptoms with much inter-individual variation. A comparison of traits defining, nearly universal to, or commonly found in autism with those known to arise from mercury poisoning which are provided in Table 1 are startlingly similar.

Table 1
Summary Comparison of Traits of Autism and Mercury Poisoning.

Psychiatric Disturbances
Social deficits, shyness, social withdrawal
Repetitive, perseverative, stereotypic behaviors; obsessive-compulsive tendencies
Depression; depressive traits, mood swings, flat affect, impaired face recognition
Anxiety; schizoid tendencies; irrational fears
Irritability, aggression, temper tantrums
Lacks eye contact; impaired visual fixation (Mercury)/problems in joint attention (Autism)

[2] Autism Society of America, *Autism Definition*, compiled from Diagnostic and Statistical Manual of Mental Disorders.

Table 1
Summary Comparison of Traits of Autism and Mercury Poisoning. (continued)

Speech and Language Deficits
Loss of speech, delayed language, failure to develop speech
Dysanthria; articulation; articulation problems
Speech comprehension deficits
Verbalizing and word retrieval problems (mercury), echolalia, word use and pragmatic errors (Autism)
Sensory Abnormalities
Abnormal sensation in mouth and extremities
Sound sensitivity; mild to profound hearing loss
Abnormal touch sensations; touch aversion
Over-sensitivity to light, blurred vision
Motor Disorders
Flapping, myocional jerks, choreiform movements, circling, rocking, toe walking, unusual postures
Deficits in eye-hand coordination; limb apraxia; intention tremors (mercury)/problems with intentional movement or imitation (Autism)
Abnormal gait and posture, clumsiness and in coordination; difficulties sitting, lying, crawling, and walking problem on one side of body.
Cognitive Impairments
Borderline intelligence, mental retardation – some cases reversible
Poor concentration, attention response inhibition (mercury)/ shifting attention (Autism)
Uneven performance on IQ subtests; verbal IQ higher than performance IQ
Poor short term, verbal and auditory memory
Poor visual and perceptual motor skills; impairment in simple reaction time (mercury)/ lower performance on timed tests (Autism)
Deficits in understanding abstract ideas & symbolism; degeneration of higher mental powers (mercury)/sequencing, planning and organizing (autism); difficulty carrying out complex commands
Unusual Behaviors
Self-Injurious behavior e.g head banging
ADHD traits
Agitation, unprovoked crying, grimacing, staring spells
Sleep difficulties
Physical Disturbances
Hyper-hypotonia; abnormal reflexes, decreased muscle strength, especially upper body; incontinence; problems chewing, swallowing
Rashes, dermatitis, eczema, itching
Diarrhea; abdominal pain/discomfort, constipation, 'colitis'
Anorexia, nausea (mercury), vomiting (autism); poor appetite (mercury)/ restricted diet (Autism)
Lesions of ileum and colon; increased gut permeability

Table 2
Summary of Comparison of Biological Abnormalities in Autism and Mercury Exposure[3]

Mercury Exposure	Autism
Biochemistry	
Binds – SH groups; blocks sulfate transporter in intestines and kidneys.	Low sulfate levels
Reduces glutathione availability; inhibits enzymes of glutathione metabolism; glutathione needed in neurons, cells, and liver to detoxify heavy metals; reduces glutathione peroxidase and reductase.	Low levels of glutathione; decreased ability of liver to detoxify xenobiotics; abnormal glutathione peroxidase activity in erythrocytes.
Disrupts purine and pyrimidine metabolism	Purine and pyromidine metabolism errors lead to autistic features.
Disrupts mitochondrial activities especially in the brain.	Mitochondrial dysfunction, especially in brain.
Immune System	
Sensitive individuals more likely to have allergies, asthma, autoimmune-like symptoms, especially rheumatoid-like ones.	More likely to have allergies and asthma; familial presence of autoimmune diseases, especially rheumatoid arthritis; IgA deficiencies
Can produce an immune response in CNS; causes brain/ MBP autoantibodies	On-going immune response in CNS; brain/MBP autoantibodies present
Causes overproduction of TH2 subset; kills/inhibits lymphocytes, T-cells, and monocytes; decreases NK T-cell activity; induces or suppresses IFNg & IL-2	Skewed immune-cell subset in the Th2 direction; decreased responses to T-cell mitogens; reduced NK T-cell function; increased IFNg & IL-12
CNS Structure	
Selectively targets brain areas unable to detoxify or reduce mercury-induced oxidative stress	Specific areas of brain pathology; many functions spared
Accumulates in amygdale, hippocampus, basal ganglia, cerebral cortex; damages Purkinje and granule cells in cerebellum; brain stem defects in some cases.	Pathology of amygdale, hippocampus, basal ganglia, cerebral cortex; damage to Purkinje and granule cells in cerebellum; brain stem defects in some cases
Causes abnormal neuronal cytoarchitecture; disrupts neuronal migration, microtubules, and cell division; reduces NCAMs	Neuronal disorganization; increased neuronal cell replication, increased glial cells; depressed expression of NCAMs
Progressive microencephaly.	Progressive microencephaly and macrocephaly

[3] Bernard et al, *Autism: a novel form of mercury poisoning*, Medical Hypotheses (2001) 56(4), 462–471

Table 2
Summary of Comparison of Biological Abnormalities in Autism and Mercury Exposure[4] (continued)

Neurochemistry	
Prevents presynaptic serotonin release and inhibits serotonin transport; causes calcium disruptions	Decreased serotonin sythesis in children; abnormal calcium metabolism
Alters dopamine systems; peroxidine deficiency in rats resembles mercurialism in humans	Either high or low dopamine levels; positive response to peroxidine, which lowers dopamine levels
Neurochemistry (continued)	
Elevates epinephrine and norepinephrine levels by blocking enzyme that degrades epinephrine	Elevated norepinephrine and epinephrine
Elevates glutamate	Elevated glutamate and aspirate
Leads to cortical acetylcholine deficiency; increases muscarinic receptor density in hippocampus and cerebellum	Cortical acetylcholine deficiency; reduced muscarinic receptor binding in hippocampus
Causes demyelinating neuropathy	Demylination in brain
Neurophysiology	
Causes abnormal EEGs, epileptiform activity, variable patterns, e.g., subtle, low amplitude seizure activities.	Abnormal EEGs epileptiform activity, variable patterns, including subtle, low amplitude seizure activities
Causes abnormal vestibular nystagmus responses; loss of sense of position in space	Abnormal vestigular nystagmus responses; loss of sense of position in space
Results in autonomic disturbance; excessive sweating poor circulation, elevated heart rate	Autonomic disturbance; unusual sweating, poor circulation, elevated heart rate

The Autism Epidemic

First, it is important to understand that autism is not a specific disease process with well-defined biological markers. Rather the condition itself is an hypothesis, "a suggestion that behind the behavioral description [lies] a disease entity."[5] In short, the absence of other biological explanation of the condition calls for the diagnoses to be provided.

Since 1943 when Dr. Leo Kanner first described Autism and provided a diagnostic criterion, there has been much discussion about both the prevalence of autism and the diagnostic criteria. Early estimates placed the prevalence of 'infantile autism' at 4.5 to 5 per 10,000 live births. Through the 1960s and 1970s, prevalence rates grew at a steady pace. In the late 1970's,

[4] Bernard et al, *Autism: a novel form of mercury poisoning*, Medical Hypotheses (2001) 56(4), 462–471

[5] Rutter M. Diagnosis and definition. In: Rutter M, Schopler E, editors. Autism: a reappraisal of concepts and treatments. New York: Plenum Press; 1978. p. 1-25 (as noted in Blaxill, *What's going on? The question of time trends in autism*, -in press-)

researchers painted a more detailed picture, including sub-definitions in the autism label that expanded upon Kanner's original parameters. The medical community began utilizing the terms Autism Spectrum Disorders (ASD) and subcategories of Asperger's syndrome, pervasive development disorder, and regressive autism. Expected increase prevalence was noted bringing the rates up to 20 per 10,000 live births. At the time Congress initiated its investigation into the potential link between thimerosal and autism, the National Institutes of Health (NIH) estimated the rates of autism at 1 in 500. By 2002, the NIH had updated its estimate to 1 in 250.

Six decades have now passed since following Kanner's effort. In the first four following decades Kanner's applied definition to the autism condition stood without much discussion or modification. In the most recent two decades, there have been efforts undertaken to better qualify the term, sub-terms, and associated or similar processes.

These efforts have fueled debate regarding recognition of actual upward trends in autism, and thus an acceptance of the "epidemic" nomenclature. Multiple studies and reviews have failed to achieve a universal perspective of various datasets and cohorts, primarily because of a universal disconnect on analysis criteria.

Further, expected evolutionary refinement of coding in universal references such as the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) or *International Classification of Diseases* (ICD) have further debate as to whether shifts in prevalence are attributable to changes in specific definition. Again, the lack of clarity to specific biological markers to provide guidance in diagnoses further confounds the matter as in the end, there is a reliance upon clinical subjectivity in providing diagnosis and coding.

Confounding the debate has been the "progressive" trends in changes and acceptance in definitions including autism, early infantile autism, infantile autism, pervasive development disorder (or PDD), childhood autism, autistic disorder, atypical PDD, PDD-NOS (not otherwise specified), autism spectrum disorders, Asperger's syndrome, childhood disintegrative disorder, and Rhett's syndrome.

Public health officials, policymakers and the public rely upon published research to provide guidance in their understanding of the issues and charting the course for the future. Even this may prove a disservice at times. In one example, three separate Scandinavian[6,7,8] epidemiological studies were published over a three year period, each reviewing prevalence and trends in autism. These studies cooperatively purported to show an evidentiary failure to support the position of an epidemic labeling of the autism situation. Further investigation into each of the individual studies design, methodology and definitions provides the insights necessary to understand that the projected impression is false.

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[6] Kadesjo B, Gillberg C, Hagberg B. Brief report: autism and Asperger syndrome in seven-year-old children: a total population study. J Autism Dev Disord 1999;29:327-31.

[7] Arvidsson T, Danielsson B, Forsberg P, Gillberg C, Johansson M, Kjellgren G. Autism in 3–6 year-old children in a suburb of Goteborg, Sweden. Autism 1997;1:163-73.

[8] Sponheim E, Skjedal O. Autism and related disorders: epidemiological findings in a Norwegian study using ICD-10 diagnostic criteria. J Autism Dev Disord 1998;28:217-27.

As an example: a 1997 Swedish study[9] measured the prevalence of autism in a 3- to 6-year-old cohort born in 1988–1991. Two years later, a second Swedish study[10] reviewed 7-year-olds in the 1985 birth cohort. A third study from Norway[11] covered a wide age range cohort and incorporated data ranging back to 1978. Unfortunately, the timing of publications and the individual stated findings provided the appearance that, at best, the prevalence of autism in Scandinavia was in constant unpredictable flux. Had the studies standardized in their methodology, meta-analyses and birth cohorts, a more accurate, and useful, presentation would have been provided.

In reviewing several similarly biased studies, Blaxill[12] specifically addresses the individual failures of the above-referenced and similar studies use of flawed, non-standardized analyses in forwarding what eventually become deeply flawed published studies. In an excerpt from his conclusions, Blaxill offers:

> *"The evidence supporting an increasing rate of autism in the U.K. and the U.S. has gathered strength. Although both the nomenclature and the criteria set used to define autism have changed over the years, these changes are not so great as to prevent comparative analysis and do not explain major differences in reported prevalence over time. The largest stable source of variability in reported autism rates comes from incomplete ascertainment in young age cohorts, which limits the ability to detect an underlying and rising secular trend. Reviews that have downplayed the rising trend have overemphasized unimportant methodological problems, employed flawed meta-analytic methods, and failed to take into account the most relevant biases in survey methodologies. Point prevalence comparisons made within and across surveys conducted in specific geographic areas, using year of birth as a reference for trend assessment, provide the best basis for inferring disease frequency trends from multiple surveys. A comparison of U.K. and U.S. surveys, taking into consideration changing definitions, ascertainment bias, and case-finding methods, provides strong support for a conclusion of rising disease frequency. The rate of autism in the U.S., once reported as less than 3 per 10,000, has now risen to more than 30 per 10,000, a 10-fold increase. The rate of autism in the U.K., once reported as less than 10 per 10,000, has risen to roughly 30 per 10,000. Reported rates for ASDs in both countries have risen from the 5–10 per 10,000 range to the 50–80 per 10,000 range. This review has found little evidence that systematic changes in survey methods can explain these increases, although better ascertainment may still account for part of the observed changes. A precautionary approach therefore suggests that increased rates of autism and related disorders be accepted as an urgent public health concern."*[13]

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[9] Arvidsson T, Danielsson B, Forsberg P, Gillberg C, Johansson M, Kjellgren G. Autism in 3–6 year-old children in a suburb of Goteborg, Sweden. Autism 1997;1:163-73

[10] Kadesjo B, Gillberg C, Hagberg B. Brief report: autism and Asperger syndrome in seven-year-old children: a total population study. J Autism Dev Disord 1999;29:327-31.

[11] Sponheim E, Skjedal O. Autism and related disorders: epidemiological findings in a Norwegian study using ICD-10 diagnostic criteria. J Autism Dev Disord 1998;28:217-27.

[12] Blaxill, *What's going on? The question of time trends in autism*, (-in press-)

[13] Blaxill, *What's going on? The question of time trends in autism*, (-in press-)

Confounding the autism epidemic discussion further are a frequent reliance, especially by government agencies, upon studies which may provide fairly accurate sources of data and assessment of the U.S. prevalence of autism, while providing inaccurate and unfounded conclusions based upon that information. Two such examples follow.

In 1996, a study conducted in metropolitan Atlanta, Georgia found that the prevalence of autism in children ages 3 to 10 was 3.4 per 1,000.[14] While making an unsubstantiated argument against a mercury/vaccine-NDD/autism link, it appears to be one of the most current and widely accepted quantifications of U.S. autism prevalence.
Two sources of data give a fairly accurate assessment of the true U.S. prevalence of autism.

A citizen's group in Brick Township, New Jersey contacted the New Jersey Department of Health and Senior Services (DHSS) in late 1997 with concerns about an apparently larger than expected number of children with autism in Brick Township. Because of the complexity of the disorder and the citizens' concern that environmental factors might play a role, the New Jersey DHSS, U.S. Senator Robert Torricelli, and U.S. Representative Christopher Smith contacted the Centers for Disease Control and Prevention (CDC) and the Agency for Toxic Substances and Disease Registry (ATSDR) for assistance. In response, a four-part plan was developed, including a prevalence investigation, a literature review of environmental factors associated with autism, an investigation of environmental pathways for human exposure in the community, and community education and involvement activities. The study found a prevalence rate of 6.7 per 1,000 children ages 3 to 10 years. In looking at environmental factors that may have contributed to this rate, the ASTDR listed mercury at a rate of 2 parts per billion being scientifically validated to be linked to the onset of autism.[15] The CDC opted not to evaluate immunization records, even though the parents in Brick Township requested that this be included in the analysis. A valuable opportunity was lost in 1998 to evaluate the potential link between immunization and autism, including the level of thimerosal in immunizations delivered in Brick Township.

In both studies, the CDC found that the rates were higher than studies in the 1980s and early 1990s.[16] Of importance is the fact that while the Atlanta study was conducted in 1996, it was not published until 2003, well after the Brick Township report had been released in 2000 and the furor around its findings died down.

Researchers out of California, where the rates of the most severe form of autism have increased by 826%[17] are firm in stating that these cases are not 'better diagnostics' and are not the result of an expanded diagnostic criteria, that there is a true dramatic increase in the incidence of late onset or regressive autism. Current rates of prevalence have been calculated at rates ranging from 34-60 per 10,000 to 1 in 100 or higher.

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[14] Yeargin-Allsopp M, Rice C, Karapurkar T, Doernberg N, Boyle C, Murphy C., "Prevalence of autism in a US metropolitan area " JAMA. 2003 Jan 1;289(1):49-55

[15] "Prevalence of Autism in Brick Township, New Jersey, 1998: Community Report, Centers for Disease Control and Prevention, April 2000"

[16] "Prevalence of Autism in Brick Township, New Jersey, 1998: Community Report, Centers for Disease Control and Prevention, April 2000"

[17] California Department of Developmental Services, "Autism Spectrum Disorders, Changes in the California Caseload, An Update", April 2003

While epidemiology and prevalence rates are important, too much energy and Federal funding has focused on determining 'how big is big' rather than addressing the underlying causes of the epidemic. Too much time has been spent attempting to use epidemiology in an attempt to disprove theories based in clinical and laboratory research, and too little effort has been put forward to truly understand the true pharmacokinetic nature of the toxic substance thimerosal.

Regardless of the number chosen for review, no one can deny that a conservative estimate of an 700% to 1200% overall increase, or up to a 48,600% regional increase, within one generation's life span, is anything less than disturbing.

Current statistics from the NIH, CDC, US Department of Education and the Autism Society of America (ASA) provide for 1-1.5 million Americans currently diagnosed with autism. It is recognized as the fastest growing developmental disability facing the American population. In comparison with overall increases in population through the 1990s, autism's growth rate was 172% vs. 13% for the population. In a similar comparison for all other disabilities, autism grew over ten times faster during the same period.

Because of the insidious and utterly destructive nature of the disease, treatment and services cost over $90 Billion in FY2003 nationally. Over ninety percent of those monies are for adult services and treatment. If we look at the lifetime lost productivity of those currently diagnosed (2003 statistics) with autism, there is a potential loss of over $7.5 Trillion to the American economy alone.

With these base statistics before us, is it any question that Mercury was the god of thievery? Since its introduction as a medical device component, millions of productive lives and billions of dollars have been stolen from American families.

Much effort has been given to the diagnoses and treatment for autism spectrum disorders, PDD, and the like. This treatise looks specifically to further explore the links between medical mercury exposure and those diseases and their myriad impacts on American families and American society. This effort will also review and report on the recent scientific efforts that have furthered a causal link between these conditions and medical mercury.

The Costs Associated with the Autism Epidemic

In 2000, in the United Kingdom Knapp and Jarbrink published an extensive review of the economic impact of autism spectrum disorders[18] While specifically tied to the situation in the United Kingdom, their event-cost modeling is now the widely accepted standard for calculating autism spectrum and related disorders. The Knapp and Jarbrink model is unique in that it looked at the entire picture of autism:

1. Pediatric and Adult Life Expenses included.

[18] Jarbrink, K. & Knapp, M. (2000). *'The economic burden of autism in Britain'*

2. Consideration for the varying costs on the Autism spectrum, from Asperger's or high functioning to very severe forms of autism.
3. Reviewed and included employment and compensation comparisons along with ratios of productivity for those with autism who manage to enter the workplace.
4. They included realized and potentials regarding effective therapies, which provided for some measure of recovery/management and allowed for children to reenter mainstream educational models and the cost-benefit relationship within.[19]

A key finding in the Knapp/Jabrink study was the global failure to evaluate the economic impact over the lifespan and to address this impact for individuals, families, and government. In addition to the driving force of compassion, the impetuous to achieve early intervention and provide support to the entire family, not just the individual, was the extent of lost productivity and quantified burdens on limited family, and government resources.

Utilizing Knapp and Jarbrink's model, the expenditures of personal and government funds for FY 2004 will exceed $100 Billion for treatment alone.[20] At the same time, the United States, through the National Institutes of Health, has scheduled an average of only $58 per child[21] (FY2003-2004) to be spent toward autism spectrum and related disorders research. Additionally, these monies are to be divided between causal and treatment research.

With the current American school age population living daily with autism spectrum or related disorders exceeding 188,000,[22] this hardly seems to represent the NIH as holding these issues as a high priority. Even the fact that the current level represents a 22-fold increase over the past ten years[23] has apparently not moved this issue further forward, nor does the fact that there is a recent historical trend for a 10-17%[24] annual increase in diagnoses of autism spectrum or related diseases.

In addition to the financial strain of autism spectrum disorders on families, school systems, the insurance industry, and state and federal agencies, having a family member affected by autism extracts a significant human toll as well. The divorce rate is reported to be 85%,[25] other siblings do without the attention of their parents, and as reported in a study from Taiwan[26] mothers with autistic children experience greater suffering than those having children with other chronic diseases such as Down's Syndrome.

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[19] Jarbrink, K. & Knapp, M. (2000). *'The economic burden of autism in Britain'*

[20] Unlocking Autism 2004, extrapolated

[21] US Department of Health & Human Services, National Institutes of Health, *Estimates of Funding for Various Diseases, Conditions, Research Areas FY2003-2005* –and- Centers for Disease Control and Prevention, National Center for Health Statistics, *Fast Stats*

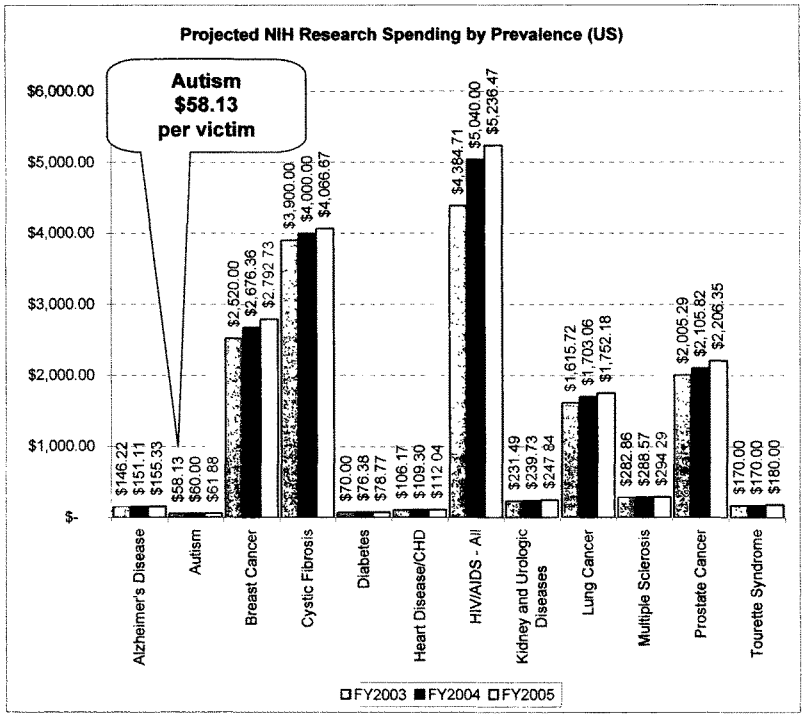
[22] US Department of Education, Annual Reports to Congress (IDEA) 1991-2003

[23] US Department of Education, Annual Reports to Congress (IDEA) 1991-2003 - extrapolated

[24] US Department of Education, Annual Reports to Congress (IDEA) 1991-2003

[25] James Jeffrey Bradstreet,MD, FAAFP, Clinical DirectorThe International Child Development Resource Center, Testimony before the US House of Representatives, Committee on Government Reform - Vaccine Safety and Autism, June 19, 2002

[26] Shu BC; Lung FW; Chang YY, The mental health in mothers with autistic children: a case-control study in southern Taiwan. Kaohsiung J Med Sci (China 2000 Jun;16(6):308-14



In addition to the looming economic disaster looming, these human tolls underscore the importance of the latest data from the California State Department of Developmental Services (DDS), California's developmental services system showing first ever nine month sustained reduction in the numbers of professionally diagnosed new cases of full syndrome autism being added to California's developmental services system. The data compares new intakes from the most current three consecutive quarterly periods (October 2003 through June 2004) to all other previous October through June time periods. Not only did the most recent three consecutive quarter periods produce the first sustained reduction in the 35 year history of California's developmental services system (197 fewer new cases then the previous October through June period), but the most current recently completed quarter, April 2004 through June 2004, produced the all time largest reduction of any quarter (108 less cases) in the history of the system.

It is important to note that DDS only reports professionally diagnosed cases of full syndrome DSM IV autism and does not include PDD, NOS, Asperger's Syndrome, or any other autism spectrum disorder in this reporting category. The numbers reported by DDS do not include children under the age of three years. Children born in the years 1999 and 2000 are now entering the system. It is this birth cohort that was born in the beginning of the serious effort to substantially reduce the amount of the mercury containing preservative Thimerosal in childhood vaccines. California, with what some perceive as the world's best record keeping system relevant to autism, is the de facto "canary in the coal mine" in tracking new cases of autism in the United States. In 1999 the first DDS report on autism established for the first time the existence of epidemic growth in the rates of autism. A report released by DDS in 2003 documented a doubling of the autism caseload from 1999-2002.[27]

Medical Exposures to Mercury

While the etiology regarding Autism Spectrum Disorders (ASD) has yet to be fully understood, research has provided benefit by identifying clearly defined links. One of those standouts has been the relationship between mercury exposure and the development of an ASD.

Mercury had long been involved in various respected and questionable treatments of various ailments. In the late 19th and early 20th centuries, mercury was formulated into teething powders for infants. It was also mixed into a variety of "cure alls" and sold through various respected and questionable outlets.

Mercury itself is an elemental metal with an atomic number of 80. Commonly referred to as "quicksilver" it has amazed adults and children alike for centuries being one of only two metals that is a liquid at room temperature. Various formulations of mercury have been involved in functions from making striking vermillion paint (mercuric sulfide), detonating explosives (mercury fulminate), and making either a corrosive and violent poison or a medical product (mercury chloride).[28]

In 2001 when nominating thimerosal to the National Toxicology Program, FDA staff admitted the following gaps in knowledge[29]:

⇒ Toxicokinetics
⇒ Ethyl vs. Methylmercury
⇒ Developmental neurotoxicity
⇒ Neurodevelopmental outcomes in children exposed to thimerosal in vaccines

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[27] Autism Spectrum Disorders, Changes in the California Caseload, An Update: 1999-2003, California Department of Developmental Services, April 2003
[28] Wikipedia, *Mercury (element)*
[29] Thimerosal Nomination Package to the National Toxicology Program http://ntp-server.niehs.nih.gov/htdocs/Chem_Background/ExSumPDF/Thimerosal.pdf

In this nomination package, HHS stated that their job was to:

> *"Make predictions about the circumstances under which a particular compound will be toxic to humans. Ideally: The data needed to make such predictions are obtained from laboratory animal models in controlled experiments under known conditions of exposure prior to the occurrence of human exposures. The use of appropriate animal models is critical. Relevant endpoints decrease uncertainty associated with the process."*[30]

The statements provide herein are incongruent with the actual actions and public statements of FDA and CDC personnel in which epidemiology has taken precedent over laboratory data and uncontrolled studies have been funded and relied upon. The result is that the answers the American public deserve have not been achieved.

Thimerosal, the Ethyl Versus Methyl Quandary

The primary issue, of late and recent history, concerning mercury laden medical products surrounds thimerosal also known as Merthiolate. Thimerosal is a preservative solution that was developed and instituted for use in the 1930s to be included in many vaccines, especially pediatric vaccines.

"Thimerosal was developed by Dr. Morris Kharasch (1895-1957; Ukraine/USA), a chemist and Eli Lilly fellow first at the University of Maryland (1922-1927) and then at the University of Chicago. He filed for a patent on June 27, 1929, for what he described as an alkyl mercuric sulfur compound (thimerosal), which he felt had potential as an antiseptic and antibacterial product. Dr. Kharasch was considered a pioneer in his field, contributing to the development of plastics and the creation of synthetic rubber. He also went on to found the *Journal of Organic Chemistry*.[31]

In October 1929, Eli Lilly and Company registered thimerosal under the trade name Merthiolate. Merthiolate was used to kill bacteria and prevent contamination in antiseptic ointments, creams, jellies, and sprays used by consumers and in hospitals. Thimerosal was also used in nasal sprays, eye drops, contact lens solutions, immunoglobulins, and most importantly here - vaccines.

Thimerosal was patented the same year that Alexander Fleming discovered penicillin. It would take more than a decade for penicillin to be fully developed, and large-scale production to begin, thimerosal was widely used in the interim. To the medical profession, who were without antibiotics during the 1930's and 1940's, thimerosal (marketed as Merthiolate) and other antiseptic products were gladly received."[32]

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[30] Thimerosal Nomination Package to the National Toxicology Program http://ntp-server.niehs.nih.gov/htdocs/Chem_Background/ExSumPDF/Thimerosal.pdf

[31] http://search.biography.com/print_record.pl?id=16530

[32] Mercury in Medicine: Are We Taking Unnecessary Risks – Hearing before the Committee on Government Reform, US House of Representatives, 106th Congress, 2nd Session, July 18, 2000, Serial Number: 106-232

Thimerosal (ethyl mercury salicylate) is an organic form of mercury that is usually introduced intramuscularly (injection).[33] In the seventy-plus years of use of thimerosal, NIH still lists as "not known" the results of exposure, side effects of exposure and period most sensitive to exposure.[34] In numerous publications, researchers suggested that caution be taken in human exposure, as early as 1934 one scientist noted, "little is known about the mercuric compounds when inoculated into humans. It is therefore preferable to use the minimum amount of this preservative."[35]

One of the most exasperating facets of the current discourse regarding mercury laden medical products is the lack of either unity, or shared science, among government agencies regarding ethyl mercury salicylate. From one set of agencies (FDA, CDC) the public receives the message that this chemical formulation provides an acceptable exposure to mercury. Even within the FDA there is a dichotomy of opinions as the Center for Drug Evaluation and Research (CDER) banned topical thimerosal because of concern about the dangers of mercury exposure through its use while the Center for Biologics Evaluation and Research allowed its increased use in infants beginning at the day of birth. The US Department of Transportation, however, lists as potential hazards in its Emergency response Guidebook 2000, that the substance is "highly toxic, may be fatal if swallowed or absorbed through skin."[36] Additionally, the NIH leads a major initiative known as the Mad as a Hatter Campaign to improve awareness of mercury hazards and reduce use of mercury at all NIH facilities. The effort builds on the successful mercury reduction campaign recently conducted by the Warren G. Magnuson Clinical Center (CC) at the NIH.[37]

Taken from
ATSDR Public Health Statement for Mercury

"Study results also suggest that reactions involving the immune system may occur in sensitive populations after swallowing inorganic mercury...

"Some animal studies report that nervous system damage occurs after long-term exposure to high levels of inorganic mercury [i.e. thimerosal]. Short-term, high-level exposure of laboratory animals to inorganic mercury has been shown to affect the developing fetus and may cause termination of the pregnancy."[38]

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[33] National Institute of Allergy and Infectious Diseases, *NIAID Research on Thimerosal*, December 2003
[34] National Institute of Allergy and Infectious Diseases, *NIAID Research on Thimerosal*, December 2003
[35] Rosenstein, Carolyn et.al.; "The Bactericidal and Antiseptic Action of Preservatives Frequently Used in Biological Products, and the Effect of these Preservatives on the Potencies of These Products;" The American Journal of Hygiene; September 31, 1934.
[36] US Department of Transportation, *ERG2000*, Guide 151, Page 266
[37] The intent of this campaign is to eliminate all unnecessary uses of mercury and reduce potential releases of mercury from unavoidable uses to the lowest level that can be reasonably be achieved.
[38] Public Health Statement for Mercury, Agency for Toxic Substances and Disease Registry, 7439-97-6

In April 2001, HHS staff conducted a literature review in order to nominate thimerosal to the National Toxicology Program. In this document, they conclude:

> *Limited data were found on the comparative toxicology of ethylmercury vs. methylmercury. One animal study directly compared the toxicity of these compounds in rats administered 5 daily doses (8.0 or 9.6 mg/kg) of equimolar concentrations of ethyl- or methylmercury by gavage. Tissue distribution, and the extent and severity of histological changes in the brain and kidney were assessed. Neurotoxicity of ethyl and methylmercury was similar, with higher levels of inorganic mercury observed in the brains of ethylmercury treated rats. Renal damage was greater in rats receiving ethylmercury. Although the data are limited, similar toxicological profiles between ethylmercury and methylmercury raise the possibility that neurotoxicity may also occur at low doses of thimerosal.*[39]

The National Toxicology Program (NTP) is an interagency program consisting of relevant toxicology activities of the National Institutes of Health's National Institute of Environmental Health Sciences (NIH/NIEHS), the Centers for Disease Control and Prevention's National Institute for Occupational Safety and Health (CDC/ NIOSH), and the Food and Drug Administration's National Center for Toxicological Research (FDA/NCTR). The National Toxicology Program (NTP) was established in 1978 by the Department of Health and Human Services (DHHS) to coordinate toxicological testing programs within the Department, strengthen the science base in toxicology; develop and validate improved testing methods; and provide information about potentially toxic chemicals to health regulatory and research agencies, the scientific and medical communities, and the public. The Program is administered by the NTP Director, who is also the Director of the NIEHS. [40]

> *Thimerosal is nominated to the NTP for further study to assess gaps in knowledge regarding toxicokinetics and the potential for neurodevelopmental toxicity. These gaps include comparative toxicity of ethyl- and methylmercury, the metabolism and elimination of ethylmercury compared with methylmercury, the effect of intermittent intramuscular doses of thimerosal from vaccines compared with chronic low dose oral exposure to methylmercury, and the susceptibility of the infant compared with the fetus to adverse effects from organicmercurials. In order to provide a more complete assessment of the toxicity of thimerosal during the critical period of neurodevelopment, well-designed studies are needed to address these gaps in knowledge in appropriate animal model(s).*[41]

For Thimerosal, the NTP as of September 1, 2004 posts the following information:

⇒ No bioassay studies are available evaluating standard toxicology and carcinogenesis
⇒ No reproductive studies are available

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[39] Thimerosal Nomination to the National Toxicology Program http://ntp-server.niehs.nih.gov/htdocs/Chem_Background/ExSumPDF/Thimerosal.pdf
[40] http://ntp-server.niehs.nih.gov/main_pages/about_NTP.html
[41] Thimerosal Nomination to the National Toxicology Program http://ntp-server.niehs.nih.gov/htdocs/Chem_Background/ExSumPDF/Thimerosal.pdf

⇒ No developmental studies available
⇒ No immunologoy studies are available
⇒ In 1983, one *in vitro* salmonella study was conducted evaluating genetic toxicity for hamsters and rats (which was negative)

A further search of the NTP sites finds that of the more than 8,000 chemicals in the market-place, zero have been approved for general toxicology study by the program. After more than 3 years of waiting, thimerosal has yet to hit the radar of the NTP. There are currently 31 chemicals with a project leader assigned and a study in design – thimerosal is not among them.

In April of 2000, Bernard et al[42] put forth the first definitive work reviewing the link between mercury and Autism Spectrum Disorders. In review, and more accurately, this effort showed that the autism presentation is a mirror to mercury toxicity.

Bernard et al[43] first showed the tabulations of total amounts of mercury exposure pediatric patients receive through a routine schedule of immunizations. That schedule for exposure, if fulfilled, would exceed EPA recommendations 100 times, often in a single office visit.

This effort sparked concerns on several levels of the health care and governmental structures of the United States, and the impact rippled worldwide. It also drew the attention of the United States House of Representatives, Committee on Government Reform. Then Chairman Dan Burton, who was in the midst of a vaccine safety oversight investigation, convened a hearing on July 18, 2000, to look into the relationship between vaccine exposures to mercury and the onset of the symptoms of autism spectrum disorders.

Chairman Burton opened the hearing presenting several points of concern for the Committee which the witnesses scheduled to testify were asked to address. The first issue Chairman Burton focused upon was a perceived failure within the agencies of Department of Health and Human Services (HHS) in touting the efficacy and safety of thimerosal containing vaccines, but had (to that date) failed or refused to convene a scientific panel to review the best data available, nor to conduct appropriate pharmacokinetic research on the issue. The Committee would later learn that HHS had conducted a secret meeting the month prior in which they reviewed a CDC study within the Vaccine Safety Datalink Program that found a statistically significant link between thimerosal exposure through vaccines in the first six months of life and tics, ADD, speech and language delays, and neurodevelopmental delays.

The next issue reviewed was of the regular exceeding of EPA maximum safety level for mercury exposure from a single pediatrician visit.[44] While the EPA set the maximum safe exposure rate for mercury exposure at 0.1 micrograms per kilogram per day (mcg/kg/day), the FDA

[42] Bernard et al, *Autism: A unique type of mercury poisoning*, April 3, 2000
[43] Bernard et al, *Autism: A unique type of mercury poisoning*, April 3, 2000
[44] Mercury in Medicine: Are We Taking Unnecessary Risks – Hearing before the Committee on Government Reform, US House of Representatives, 106th Congress, 2nd Session, July 18, 2000, Serial Number: 106-232

acknowledged that during the first 6 months of life, this figure was frequently exceeded by over 400% through regular scheduled immunizations.[45]

The third focus of the committee hearing was the apparent disconnect between the FDA and EPA regarding the maximum safe exposure level for mercury. The FDA, at the time, was utilizing a figure for safety that was five times greater than that stated by the EPA. While there have been modifications, there (today) remains an unresolved and unexplained disparity between those agencies safety levels figures.

In 2000, a National Academy of Sciences (NAS) report[46] specifically included review for what should be deemed by appropriate agencies as the standard maximum level for mercury exposures. This figure, identified as the "lowest observed adverse event level" or LOAEL, was reviewed and measured according to the finds of several studies. It was the determination of the NAS that the EPA guidelines were far more correct and should be adopted by all relevant agencies as the maximum acceptable exposure level.

Finally, an opportunity to review much of the independent effort looking into the mercury induced injury issue was to be presented and submitted for further review.

Bernard et al's effort[47] provided a great insight to the medical mercury induced neurological injury arena, and served as the road map for nearly all subsequent discussion, from definition to epidemiology to toxicology.

A discourse between Congressman Dave Weldon, MD and Dr. David Baskin during the December 10, 2002 hearing of the Committee on Government Reform provides a fair analysis of this quandary:

Dr. Weldon. *I have a couple of questions for Dr. Baskin about ethyl mercury versus methyl mercury. I have had some people say that data on methyl mercury is fairly good, but we don't have good data on ethyl mercury. I take it from your testimony there is actually quite a bit of data on ethyl mercury and that it's as toxic as methyl mercury.*

Dr. Baskin. *There is more data, more and more data on ethyl mercury. The cells that I showed you dying in cell culture are dying from ethyl mercury. Those are human frontal brain cells. You know, there has been a debate about, well, ethyl versus methyl. But from a chemical point of view, most chemical compounds that are ethyl penetrate into cells better than methyl. Cells have a membrane on them, and the membrane is made of lipids, fats. And ethyl as a chemical compound pierces fat and penetrates fat much better than methyl. And so, you know, when I've began to work with some of the Ph.D.s in my laboratory and discuss this, everyone said, oh,*

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[45] Mercury in Medicine: Are We Taking Unnecessary Risks – Hearing before the Committee on Government Reform, US House of Representatives, 106th Congress, 2nd Session, July 18, 2000, Serial Number: 106-232

[46] Toxicological Effects of Methylmercury (2000), Commission of Life Sciences, Committee on the Toxicological Effects of Methylmercury, Board of Environmental Studies and Toxicology, National Research Council, National Academy of Sciences, ISBN 0-309-07140-2

[47] Bernard et al, *Autism: A unique type of mercury poisoning*, April 3, 2000

gosh, you know, we've got to adjust for ethyl because it's going to be worse; the levels are going to be much higher in the cells. So, I mean, I think at best they're equal, but it's probably highly likely that they are worse. And some of the results that we are seeing in cell culture would support that...[48]

The Government's Response

While the Public Health Service, within the Department of Health and Human Services were out front in announcing that thimerosal in vaccines posed, at minimum, a potential hazard, they have been remiss in focusing appropriate attention and resources to answer the concerns raised by many physicians, scientists, researchers, and United States representatives with oversight. Nor have they followed through with their own sub-agency public recommendations to create and promulgate policy for the removal of thimerosal from all pediatric vaccines.

In May 2003, the United States Congress Committee on Government Reform, Subcommittee on Human Rights and Wellness published a staff report following a three-year investigation into the mercury in medicine issue. The committee's efforts included public hearings in 2000, 2001 and 2002. At each of these hearings, the committee heard from a myriad of scientists, health care providers, researchers and parents regarding the safety, efficacy and impact of utilizing medical mercury in various medicines and devices.

While there were numerous findings and recommendations born out of Congress' investigation of the issue, most telling to the issue was the publishing of their number one finding: "Mercury is hazardous to humans. Its use in medicinal products is undesirable, unnecessary and should be minimized or eliminated entirely."[49]

That document proved a foundation for much of the following relevant research and discussion. Following are that documents findings and conclusions:

Table of Findings – "Mercury in Medicine – Taking Unnecessary Risks" [50]

1. Mercury is hazardous to humans. Its use in medicinal products is undesirable, unnecessary and should be minimized or eliminated entirely.
2. For decades, ethylmercury was used extensively in medical products ranging from vaccines to topical ointments as preservative and an antibacteriological agent.

[48] Vaccines and the Autism Epidemic: Reviewing the Federal Governments Track Record and Charting a Course for the Future, Serial No. 107-153

[49] *Mercury in Medicine – Taking Unnecessary Risks*, A Report of the Subcommittee on Human Rights and Wellness, Committee on Government Reform, United States House of Representatives, Dan Burton, Chairman, May 2003,

[50] *Mercury in Medicine – Taking Unnecessary Risks*, A Report of the Subcommittee on Human Rights and Wellness, Committee on Government Reform, United States House of Representatives, Dan Burton, Chairman, May 2003,

Table of Findings – "Mercury in Medicine – Taking Unnecessary Risks" [51] **(continued)**

3. Manufacturers of vaccines and thimerosal, (an ethylmercury compound used in vaccines), have never conducted adequate testing on the safety of thimerosal. The FDA has never required manufacturers to conduct adequate safety testing on thimerosal and ethylmercury compounds.
4. Studies and papers documenting the hypoallergenicity and toxicity of thimerosal (ethylmercury) have existed for decades.
5. Autism in the United States has grown at epidemic proportions during the last decade. By some estimates the number of autistic children in the United States is growing between 10 and 17 percent per year. The medical community has been unable to determine the underlying cause(s) of this explosive growth.
6. At the same time that the incidence of autism was growing, the number of childhood vaccines containing thimerosal was growing, increasing the amount of ethylmercury to which infants were exposed threefold.
7. A growing number of scientists and researchers believe that a relationship between the increase in neurodevelopmental disorders of autism, attention deficit hyperactive disorder, and speech or language delay, and the increased use of thimerosal in vaccines is plausible and deserves more scrutiny. In 2001, the Institute of Medicine determined that such a relationship is biologically plausible, but that not enough evidence exists to support or reject this hypothesis.
8. The FDA acted too slowly to remove ethylmercury from over-the-counter products like topical ointments and skin creams. Although an advisory committee determined that ethylmercury was unsafe in these products in 1980, a rule requiring its removal was not finalized until 1998.
9. The FDA and the CDC failed in their duty to be vigilant as new vaccines containing thimerosal were approved and added to the immunization schedule. When the Hepatitis B and Haemophilus Influenzae Type b vaccines were added to the recommended schedule of childhood immunizations, the cumulative amount of ethylmercury to which children were exposed nearly tripled.
10. The amount of ethylmercury to which children were exposed through vaccines prior to the 1999 announcement exceeded two safety thresholds established by the Federal government for a closely related substance – methylmercury. While the Federal Government has established no safety threshold for ethylmercury, experts agree that the methylmercury guidelines are a good substitute. Federal health officials have conceded that the amount of thimerosal in vaccines exceeded the EPA threshold of 0.1 micrograms per kilogram of bodyweight. In fact, the amount of mercury in one dose of DTaP or Hepatitis B vaccines (25 micrograms each) exceeded this threshold many times over. Federal health officials have not conceded that this amount of thimerosal in vaccines exceeded the FDA's more relaxed threshold of 0.4 micrograms per kilogram of body weight. In most cases, however, it clearly did.

[51] *Mercury in Medicine – Taking Unnecessary Risks*, A Report of the Subcommittee on Human Rights and Wellness, Committee on Government Reform, United States House of Representatives, Dan Burton, Chairman, May 2003,

Table of Findings – "Mercury in Medicine – Taking Unnecessary Risks" [52] **(continued)**

11. The actions taken by the HHS to remove thimerosal from vaccines in 1999 were not sufficiently aggressive. As a result, thimerosal remained in some vaccines for an additional two years.
12. The CDC's failure to state a preference for thimerosal- free vaccines in 2000 and again in 2001 was an abdication of their responsibility. As a result, many children received vaccines containing thimerosal when thimerosal- free alternatives were available.
13. The Influenza vaccine appears to be the sole remaining vaccine given to children in the United States on a regular basis that contains thimerosal. Two formulations recommended for children six months of age or older continue to contain trace amounts of thimerosal. Thimerosal should be removed from these vaccines. No amount of mercury is appropriate in any childhood vaccine.
14. The CDC in general and the National Immunization Program in particular are conflicted in their duties to monitor the safety of vaccines, while also charged with the responsibility of purchasing vaccines for resale as well as promoting increased immunization rates.
15. There is inadequate research regarding ethylmercury neurotoxicity and nephrotoxicity.
16. There is inadequate research regarding the relationship between autism and the use of mercury-containing vaccines.
17. To date, studies conducted or funded by the CDC that purportedly dispute any correlation between autism and vaccine injury have been of poor design, under-powered, and fatally flawed. The CDC's rush to support and promote such research is reflective of a philosophical conflict in looking fairly at emerging theories and clinical data related to adverse reactions from vaccinations.

Table of Recommendations – "Mercury in Medicine – Taking Unnecessary Risks" [53]

1. Access by independent researchers to the Vaccine Safety Datalink database is needed for independent replication and validation of CDC studies regarding exposure of infants to mercury-containing vaccines and autism. The current process to allow access remains inadequate.

[52] *Mercury in Medicine – Taking Unnecessary Risks*, A Report of the Subcommittee on Human Rights and Wellness, Committee on Government Reform, United States House of Representatives, Dan Burton, Chairman, May 2003,

[53] *Mercury in Medicine – Taking Unnecessary Risks*, A Report of the Subcommittee on Human Rights and Wellness, Committee on Government Reform, United States House of Representatives, Dan Burton, Chairman, May 2003,

Table of Recommendations – "Mercury in Medicine – Taking Unnecessary Risks" [54] **(continued)**

2. A more integrated approach to mercury research is needed. There are different routes that mercury takes into the body, and there are different rates of absorption. Mercury bioaccumulates; the Agency for Toxic Substances and Disease Registry (ATSDR) clearly states: "*This substance may harm you.*"s Studies should be conducted that pool the results of independent research that has been done thus far, and a comprehensive approach should be developed to rid humans, animals, and the environment of this dangerous toxin.
3. Greater collaboration and cooperation between federal agencies responsible for safeguarding public health in regard to heavy metals is needed.
4. The President should announce a White House conference on autism to assemble the best scientific minds from across the country and mobilize a national effort to uncover the causes of the autism epidemic.
5. Congress needs to pass legislation to include in the National Vaccine Injury Compensation Program (NVICP) provisions to allow families who believe that their children's autism is vaccine- induced the opportunity to be included in the program. Two provisions are key: First, extending the statute of limitations as recommended by the Advisory Commission on Childhood Vaccines from 3 to 6 years. Second, establishing a one to two-year window for families, whose children were injured after 1988 but who do not fit within the statute of limitations, to have the opportunity to file under the NVICP.
6. Congress should enact legislation that prohibits federal funds from being used to provide products or pharmaceuticals that contain mercury, methylmercury, or ethylmercury unless no reasonable alternative is available.
7. Congress should direct the National Institutes of Health to give priority to research projects studying causal relationships between exposure to mercury, methylmercury, and ethylmercury to autism spectrum disorders, attention deficit disorders, Gulf War Syndrome, and Alzheimer's Disease.

While Congress' efforts have been attempting to bring a new light and resources to the issues involved, this matter remains constantly and negatively impacting people, children and families.

Congressional Hearings, Reports, and Legislation

Over the last several years, the Committee on Government Reform of the U.S. House of Representatives has reviewed the mercury in medicine and associated links with neurodevelopmental disorders. Under the leadership of Chairman Dan Burton (IN), this committee held several informational and scientific based forums to gain a better understanding of the issue, and develop the appropriate governmental response.

[54] *Mercury in Medicine – Taking Unnecessary Risks*, A Report of the Subcommittee on Human Rights and Wellness, Committee on Government Reform, United States House of Representatives, Dan Burton, Chairman, May 2003,

1999

- AUGUST 3, 1999: VACCINES--FINDING THE BALANCE BETWEEN PUBLIC SAFETY AND PERSONAL CHOICE

    - According to Chairman Burton, this hearing wished to look at, "The tension between the individual risks and the public benefit is a classic ethical dilemma for public health." He wished for this specific focus, recognizing, "Some have described the current mandating of an increasing number of vaccines to children to be a good intention gone too far."[55]

2000

- APRIL 6, 2000: AUTISM: PRESENT CHALLENGES, FUTURE NEEDS--WHY THE INCREASED RATES?

    - At this forum, Chairman Burton recognized and wished to investigate why, "the rates of autism have escalated dramatically in the last few years." Additionally, a review was called for understanding, "what used to be considered a rare disorder has become a near epidemic."[56]

- JUNE 15, 2000: FACA: CONFLICTS OF INTEREST AND VACCINE DEVELOPMENT--PRESERVING THE INTEGRITY OF THE PROCESS

    - At this hearing, the focus of governmental agency conflict of interest was reviewed. The Committee saw how various agencies, charged with facets of maintaining public health (and integrity in those processes) are actually conflicted by their mandates to promote and approve vaccine use in the United States versus their charge to maintain vaccine safety. Additionally, the question as to whether the pharmaceutical industry had too much influence over relevant public health committees. Here, Chairman Burton stated, "from the evidence we've found, we believe that they do," when he was referring to relevant FDA and CDC vaccine safety related committees. A staff report was issued and recommendations provided to the HHS Secretary.[57]

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[55] 106th Congress House Hearings, From the U.S. Government Printing Office via GPO Access, DOCID: f:62560.wais

[56] 106th Congress House Hearings, From the U.S. Government Printing Office via GPO Access, DOCID: f:69622.wais

[57] 106th Congress House Hearings, From the U.S. Government Printing Office via GPO Access, DOCID: f:73042.wais

2000 (Continued)

- JULY 18, 2000: MERCURY IN MEDICINE--ARE WE TAKING UNNECESSARY RISKS?

    - The Committee of Government Reform furthered their efforts to look into vaccine safety, especially pediatric vaccines, and the issue of thimerosal. Chairman Burton recognized that, "Vaccines are the only drugs that Americans are required by a government agency to take. It is thus imperative that the Federal Government ensures the safety of these mandated." What was found is best described as a failure to respond to a "no-brainer" (the total removal of mercury from medical products, including vaccines) by the U.S. Public Health Service and the FDA.[58]

2001

- APRIL 25 AND 26, 2001: AUTISM--WHY THE INCREASED RATES? A ONE-YEAR UPDATE

    - The Committee took additional testimony and reviewed new science and recognized/concluded that; "We have a national and potentially worldwide epidemic on our hands. It cannot simply be better reporting or an expanded definition of autism." Additionally, the Committee stated, "As with any epidemic, we need to focus significant energy and research on containing it."[59]

2002

- APRIL 18, 2002: THE AUTISM EPIDEMIC--IS THE NIH AND CDC RESPONSE ADEQUATE?

    - The Committee found a definitive lack of focus and attention at both the NIH and the CDC to the autism epidemic in the United States. This attitude was still prevalent even in the face of heightened Congressional oversight and attention. Chairman Burton stated, "I believe these numbers speak for themselves. Funding in basic and clinical research into autism needs to be expanded dramatically. We have an epidemic on our hands, and we in Congress need to make sure that the NIH and CDC treat this condition like an epidemic and put their efforts into doing several things: First, to find out the causes of the epidemic. Second, determine how to stop the epidemic in its tracks. Third, to evaluate treatment options. And, fourth, to look for a cure."[60]

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[58] 106th Congress House Hearings, From the U.S. Government Printing Office via GPO Access, DOCID: f:72722.wais

[59] 107th Congress House Hearings, From the U.S. Government Printing Office via GPO Access, DOCID: f:76856.wais

[60] 107th Congress House Hearings, From the U.S. Government Printing Office via GPO Access, DOCID: 80-356 pdf

2002

- JUNE 19, 2002: THE STATUS OF RESEARCH INTO VACCINE SAFETY AND AUTISM

    - The Committee found that (again) little research focus, attention, or funding was being directed to the issue of vaccine safety as requested by Congress. It is important to note Chairman Burton's statement, "Through a congressional mandate to review thimerosal content in medicines, the FDA learned that childhood vaccines when given according to the CDC's recommendations exposed over 8,000 children a day in the United States to levels of mercury that exceed Federal guidelines."

- DECEMBER 10, 2002: VACCINES AND THE AUTISM EPIDEMIC: REVIEWING THE FEDERAL GOVERNMENT'S TRACK RECORD AND CHARTING A COURSE FOR THE FUTURE

    - One of the most telling statements that was born out of this hearing was from David Weldon, MD (FL). Dr. Weldon showed, "If scientists behaved purely like scientists and did purely objective research all the time, then the comments [against a thimerosal-autism link] would be valid. The reality is scientists and medical researchers operate with a system of biases that frankly can be very, very politicized." The Committee went on to recognize that the US Public Health Service is subject (and responsive) to many influences, which put into jeopardy their objectivity and efforts, and put millions of children at risk.[61]

2003

- NOVEMBER 13, 2003: PREVENTING ANOTHER SV40 TRAGEDY: ARE TODAY'S VACCINE SAFETY PROTOCOLS EFFECTIVE?

    - Chairman Burton opened with a statement that portrayed to his perspective a pattern of questions and uncooperativeness with vaccine manufacturers in response to various governmental inquiries, including requests of proof of following various vaccine safety relevant practices. Burton offered, "the subcommittee has invited representatives from the FDA and several vaccine manufacturers to present evidence that supports compliance with safe manufacturing protocols... Regrettably none of the vaccine manufacturing companies chose to attend today's hearing. And because of the mandatory nature and risk associated with all human vaccines, government health agencies have a special duty to exercise the utmost care and the approval, administration and post-administration surveillance of vaccines. The

[61] 107th Congress House Hearings, From the U.S. Government Printing Office via GPO Access, DOCID: f:84605.wais

government must always err on the side of caution in this worthy public health endeavor and to do anything less is a breach of the public trust. This subcommittee will continue to pursue the historic truth in this matter to either reaffirm or, if necessary, rebuild the public's confidence in vaccines specifically and our public health service in general."[62]

- NOVEMBER 20, 2003: THE FUTURE CHALLENGES OF AUTISM: A SURVEY OF THE ONGOING INITIATIVES IN THE FEDERAL GOVERNMENT TO ADDRESS THE EPIDEMIC

    - In his opening statement, Chairman Dan Burton reviewed the most recent selected state and national government statistics regarding the Autism Spectrum Disorders epidemic. One caution that Chairman Burton put forward was "If the upward trends of autism continue, the budgetary impact could increase 40 times to over $400 billion per year by the year 2013, and that is something we can't let happen if it is at all possible..." The Committee went on to recognize a failure within the FDA and Public Health Service to review the successes, even if only anecdotal, of various heavy metal treatments such as chelation in treatment of ASD diagnosed children, and called for further rigorous research of such treatment potentials for ASD and NDD patients.[63]

Pending Legislation: HR 4169

In April 2004, Congressman David Weldon, MD (FL-15) after following the issue for five years and perceiving a lack of response from HHS introduced legislation, HR 4169 with Congresswoman Carolyn D Maloney (NY-14), "The Mercury Free Vaccine Act of 2004" to guarantee a removal of thimerosal from vaccines. As a practicing physician, he had had a keen interest in and understanding of the complexity of the thimerosal issue, including attendance and speaking at the IOM Immunization Safety Committee hearings.[64, 65]

Dr. Weldon's effort attempts to answer the two primary concerns regarding continued thimerosal exposure to infant and pediatric patients. First, as vaccine manufacturers' utilize, and claim, thimerosal solely as a preservative; and since manufacturing and distribution of thimerosal free versions is commonplace, there is no reasonable expectation or perceived need for its continued inclusion in America's vaccine arsenal.

The second issue addressed by Dr. Weldon's bill is that of immunization scheduling. While most of the vaccines on today's infant and pediatric scheduling are thimerosal free, there remain high opportunities for pre- and post-natal thimerosal exposure from "off schedule"

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[62] 107th Congress House Hearings, From the U.S. Government Printing Office via GPO Access, DOCID: f:92772.wais

[63] 107th Congress House Hearings, From the U.S. Government Printing Office via GPO Access, DOCID: f:92727.wais

[64] http://www.iom.edu/file.asp?id=19029

[65] http://thomas.loc.gov/cgi-bin/bdquery/z?d108:h.r.04169:

immunizations. These would include such examples as prenatal immunoglobulin, influenza vaccine and the Hepatitis B vaccine. Additionally, there are current movements to potentially place thimerosal laden Hepatitis A into the schedule or give it suggested status. Without a ban on the use of thimerosal, it is possible that thimerosal exposure over time could increase.

Only through the guarantee of thimerosal free vaccines offered in the Weldon Bill can the public trust begin to be restored. At present there are 31 cosponsors on the bill.

Environmental Protection Agency

The mission of the Environmental Protection Agency (EPA) is to protect human health and the environment. Since 1970, EPA has been working for a cleaner, healthier environment for the American people. EPA has been very active in reducing mercury exposures in medical environments. An example of such actions follows:

EPA published a manual entitled, "Reducing Mercury Use in Health Care 10 Best Management Practices" which it advices hospitals to

- ⇒ Phase out all nonessential uses of mercury in laboratories.
- ⇒ Eliminate the use of mercury-containing compounds in all clinical, research and teaching laboratories unless there is no alternative.
- ⇒ Eliminate all nonessential mercury devices, such as thermometers and barometers, and replace them with mercury-free devices.
- ⇒ Clear laboratories and storage areas of unnecessary mercury compounds.
- ⇒ Request mercury-free pharmaceutical supplies whenever possible.

The EPA goes on to advice: The mercury compound in a chemical formulation may be an active ingredient, a preservative, or a contaminant introduced during the manufacture of one of the ingredients. The alternative depends on the reason that mercury is present. If a mercury compound is an active ingredient, the replacement may be a compound of a less hazardous metal. If a mercury compound is a preservative, the formulation can often be replaced by a formulation that uses a non-mercury preservative. If mercury is a contaminant, a formulation can often be found with ingredients manufactured by a different method. Because mercury may be present in very small amounts as a preservative or contaminant, it may not be obvious whether or not a chemical reagent or stain contains mercury. Manufacturers might not list the ingredients of a reagent or stain if the formula is under copyright protection. Material Safety Data Sheets might not list mercury in a product if the formula is under copyright protection or if the amount is less than one percent.[66] However, the contribution of many low concentration sources accounts for a large fraction of the mercury in the wastewater stream. The hospital purchasing agent should contact the hospital's suppliers and request that mercury-free reagents be supplied. If the usual supplier cannot provide mercury-free reagents, locate one that can. Request that all vendors

[66] An Example of the Material Safety Data Sheet is provided at Appendix B

disclose mercury concentration on a Certificate of Analysis. Products with no or low mercury can then be selected for purchase. The Certificate of Analysis should list mercury content in parts per billion (ppb), not as a percentage."[67]

The full list[68] of products containing mercury in medical laboratories complied by EPA is provided at Appendix A."

Pharmaceutical Uses of Mercury	
Products	**Notes**
Merbromin/water solution	Used in plastic/reconstructive surgery as a disinfectant and marker
Opthalmic and contact lens products	May contain mercury preservatives: thimerosal, phenylmercuric acetate, phenylmercuric nitrate
Nasal Sprays	May contain mercury preservatives: thimerosal, phenylmercuric acetate, phenylmercuric nitrate
Vaccines	May contain thimerosal (primarily in hemophilus, hepatits, rabies, tetanus, influenza, diphtheria, and pertussis vaccines.)

Another disturbing statement in this report follows:

"The mercury-cell process is one of the processes that may be used to manufacture common ingredients of cleaners and degreasers: sodium hydroxide (caustic soda), potassium hydroxide, chlorine and hydrochloric acid (muriatic acid). When these chemicals are used to make other products, such as bleach or soaps, mercury contamination can be introduced into the final product."

Laboratory analyses were conducted on several common cleaners and show that mercury exposure can also occur through unsuspecting sources.[69]

Mercury Content of Selected Cleaning Products	
Product	**Mercury Content (ppb)**
Ajax Powder	0.17
Comet Cleaner	0.15
Lysol Direct	<0.011
Soft Scrub	<0.013

[67] EPA Manual http://www.epa.gov/glnpo/bnsdocs/merchealth/mercury.pdf
[68] http://www.epa.gov/seahome/mercury/src/labs.htm
[69] The laboratory analyses were conducted by the Massachusetts Water Resources Authority (MWRA) and Medical, Academic and Scientific Organizations,Inc. (MASCO) thorug a public-private partnership called the MWRA/MASCO Mercury Work Group. These tests were on limited, many common cleaning products have not been tested. Reducing Mercury Use in Health Care Page 10, http://www.epa.gov/glnpo/bnsdocs/merchealth/mercury.pdf

Mercury Content of Selected Cleaning Products	
Product	**Mercury Content (ppb)**
Alconox Soap	0.004 mg/kg, 0.005 mg/kg, <0.0025 mg/kg (3 tests)
Derma Scrub	<5.0, <2.5 (2 tests)
Dove Soap	0.0027
Ivory Dishwashing Liquid	0.061
Joy Dishwashing Liquid	<0.01
Murphy's Oil Soap	<0.012
Soft Cide Soap (Baxter)	8.1
Sparkleen Detergent	0.0086
Sunlight Dishwashing Detergent	<0.011

These findings which have not been widely acknowledged within this discussion need to be further evaluated.

The take away message for hospital personnel from the EPA: *For most mercury containing products in the hospital, the preferred best management practice is to replace the item with a mercury-free product.*

The Department of Health and Human Services

The United States Department of Health and Human Services is the umbrella department that handles nearly all of health related matters for the country through its charged agencies. Only through a cohesive/interagency can matters such as mercury in medicine be appropriately addressed.

Here has been one of the major factors leading to a disjointed, and frequently contradictory, approach to policy direction with regard to mercury/thimerosal related issues. There has been an apparent and frequent disconnect of policy, resource management and research focus, which has not only disallowed a cohesive public message, but also a unity in research review. While under Secretary Tommy Thompson, a focus on a "One HHS" approach was initiated, its premise remains unfulfilled.

Centers for Disease Control and Prevention

The CDC's primary related focus has always been for implementation of an "appropriate" immunization plan to protect and benefit the American people. The reasons for frequent slow to counter-responses from the CDC would, with intellectual honesty, almost be expected.

Americans have charged the CDC with assuring minimal opportunities for widespread disease outbreaks across our population. There is reliance upon them to accomplish this task. As such, the CDC promotes immunizations and vaccines through a multi-million dollar education and public relations campaign. Herein lies part of the problem to the CDC's sluggish responses to the thimerosal issue.

As we charge the CDC to achieve the highest opportunity for disease prevention, they are equitably charged with a portion of responsibility for the safety of the program to achieve this goal. Any interruption in the process to full compliance with immunization would be a perceived failure. Either admission to issues regarding thimerosal laden vaccines, or delays in moving to thimerosal free versions, would potentially interrupt the process, and be a perceived failure. In short, the CDC is conflicted by two duties it has been charged with: maximizing immunizations and maintaining immunization safety. A problem regarding the latter would serious hamper the efforts of the former. The thimerosal crisis has exemplified this inherent conflict, showing that long-time CDC employees will set aside the rigors of good science which to protect vaccine policies.

A great benefit to the CDC, and the national immunization efforts in general, would be the removal of the vaccine safety and monitoring component out of the CDC's realm, and to another non-conflicted public health/interest related agency. This would allow the CDC to receive free and non-conflicted advice regarding vaccine safety, and begin a large and measurable step to regaining the public trust in our immunization programs.

Currently, our nation utilizes two passive monitoring system for tracking vaccine related adverse events. The first is the VAERS (Vaccine Adverse Event Reporting System) which is a subjective effort managed by the Food and Drug Administration. The second is the VSD (Vaccine Datalink System), which is a compilation of data streams from predetermined health maintenance organizations (HMO), managed by the FDA, CDC and a contractor.

In 2000, armed with the reluctant researcher Dr. Thomas Verstraeten's VSD study[70,71] and data indicating a statistically significant correlation between the administration of thimerosal laden vaccines and the onset of tics, speech and language delays and neurodevelopmental developmental delays,[72] rather than take swift and aggressive measures to eliminate all exposures to thimerosal in children, the CDC delayed the publication of the data while conducted additional evaluations of the data, with each generation of the study, diluting the findings, until no conclusive findings would be found in the published findings.

Subsequent attempts for independent review of the VSD data have been met with numerous obstacles. One completed study by Geier and Geier,[73] corroborated Verstraeten et al's initial

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[70] Thimerosal VSD Study – Phase 1, Update 2/29/00, Thomas Verstraeten, Robert Davis, Frank Destefano, obtained via FOIA by SafeMinds, Summer 2001

[71] Scientific Review of Vaccine Safety Datalink Information, June 7-8, 2000, Simpsonwood retreat Center, Norcross, GA – Minutes of meeting obtained under FOIA by SafeMinds, Summer 2001

[72] Scientific Review of Vaccine Safety Datalink Information, June 7-8, 2000, Simpsonwood retreat Center, Norcross, GA – Minutes of meeting obtained under FOIA by SafeMinds, Summer 2001

[73] *Nuerodevelopmental Disorders after Thimerosal-Containing Vaccines: A Brief Communication*, Geier and Geier, Experimental Biology and Medicine, 2003

suspicion of an apparent epidemiological link between Thimerosal and neurodevelopmental disorders, including autism. Unfortunately, since, and some suspect due to, the Geier's efforts, HHS and CDC have placed near impenetrable restrictions on access and study types related to VSD data, and such studies are no longer available for replication.

The following is how HHS describes this study:

> *In order to assess the potential health effects of exposure to thimerosal in childhood vaccines, the Centers for Disease Control and Prevention (CDC) sought epidemiological data to examine selected outcomes with varying exposure levels of thimerosal. This "screening analysis" found weak (relative risk less than 2) but statistically-significant associations between exposure to thimerosal-containing vaccines before the age of 6 months and tic disorders, attention deficit disorders (ADD), and speech and language disorders. The investigators then used another, smaller database from the East Coast for a more focused study to test the hypotheses that tic disorders, ADD, and speech and language disorders are associated with thimerosal exposure before 6 months of age. This study did not confirm an association. Taken together, the results of the two studies are inconclusive as to an effect of thimerosal on neurological outcomes.*[74]

The public remains puzzled as why armed with the initial data by Verstraeten et al that the CDC did not aggressively move to assure that no child would be exposed to thimerosal in their vaccines and why, instead the agency's next move was to endorse a recommendation to give all children six months and older the flu vaccines, but chose not to state a preference for thimerosal-free (which is available). This and similar actions have been seen by many parents as an egregious miscarriage of their responsibility to protect children from harm.

The challenges described above regarding access to the VSD led to the CDC contracting the IOM to a committee to "Review of the National Immunization Program's Research Procedures and Data Sharing Program." The committee has been tasked to:

1. (a) review the design and the implementation to date of the new Vaccine Safety Datalink Data Sharing Program to assess compliance with the current standards of practice for data sharing in the scientific community and,
   (b) make recommendations to the National Immunization Program for any needed modifications that would facilitate use, ensure appropriate utilization, and protect confidentiality; and
2. (a) review the iterative approaches to conducting analysis that are characteristics of studies using the complex, automated Vaccine Safety Datalink system. Examples of recent studies to be examined are a completed screening study on thimerosal and vaccines (Verstraeten et al) and cohort studies on asthma. The committee will use that review to
   (b) consider whether, when, and how preliminary data about potential vaccine-related risks obtained from the Vaccine Safety Datalink system should be shared with other scientists, communicated to the public, and used to make policy or recommendations to

[74] Thimerosal Nomination to the National Toxicology Program, http://ntp-server.niehs.nih.gov/htdocs/Chem_Background/ExSumPDF/Thimerosal.pdf

CDC and
(c) make recommendations to the National Immunization Program on the release of such preliminary data in the future. A brief report with conclusions and recommendations will be issued for each of these two topics.[75]

The first meeting was conducted on August 23, 2004 in Washington, DC. During the meeting, Barbara Loe Fischer of the National Vaccine Information Center reminded the Committee the importance of utilizing the VSD to evaluate both acute and chronic conditions that existing hypotheses have emerged indicating a potential connection:

Epidemic of Chronic Illness and Disability in Children

- 1 in 6 have development delays or behavior disorders
- 3 million learning disabled schoolchildren
- 94,000 autistic schoolchildren
- 4 million with ADHD
- 9 million with asthma
- 300,000 have juvenile rheumatoid arthritis
- 1 in 400 to 500 are diabetic

Ms. Fisher left them with a quote from a decade old publication of the IOM:

"The lack of adequate data regarding many of the adverse events under study was of major concern to the committee. Presentations at public meetings indicated that many parents and physicians share this concern. in the course of its reviews additional obvious needs for research and surveillance were identified."

-Institute of Medicine Vaccine Safety Committee *Adverse Events Associated with Childhood Vaccines*, 1994

A report from the IOM's new committee is expected by early October.

Food and Drug Administration

In a written response to the July 18, 2000, Congressional hearing the FDA states that "The toxicity of mercury has been known since antiquity" The FDA also acknowledged that animal studies conducted in the 1920's showed kidney and intestinal lesions in animals associated with high levels of mercury exposure from thimerosal. Further the FDA states they do not ask for safety data specific to an inactive ingredient. In 1988 the FDA allowed the continued use of mercury compounds as inactive ingredients (preservatives) while determining that mercury compounds used as active ingredients in over-the-counter products were found not to be generally recognized as safe and effective. In this written response the FDA also states that between 1990 and 1998 they received 47 adverse events reported through the Vaccine Adverse Events Reporting System (VAERS) attributed by the reporting individual as being due to

[75] http://www.iom.edu/project.asp?id=21144

mercury or thimerosal. From 1998 to July 2000 another 15 reports were received. The FDA also reported that in July 2000 that HHS had funded only one study looking at mercury toxicity in thimerosal. This 1967 study evaluated the carcinogenicity of various chemicals used in the preparation of vaccines, including thimerosal.[76]

In reviewing the list of grants funded by FDA on the CRISP Database[77], SafeMinds learned that 33 studies had been funded between 1990 and 2003 on thimerosal. Most of these were internal studies conducted by Supervisory Chemist, Dr. Joan C. May (FDA/CBER/OVRR/ARC) with titles that included:

- ⇒ Analysis and Characterization of Mercury and Trace Elements in Injectable Products
- ⇒ Analysis and characterization of mercury in injectable products
- ⇒ Analysis of mercury in injectable products
- ⇒ Development of Organic and Inorganic Analytical Methodol
- ⇒ Experiments in Radiation Sterilization
- ⇒ Analysis and Characterization of Mercurial Preservatives in Injectables
- ⇒ Determination of Nitrogen Content (Protein) of Biological Products

A full list of these grants and their abstracts is provided at Appendix D.

It is obvious from these findings that FDA's Center for Biologics Evaluation and Research (CBER) was evaluating thimerosal for its benefit in vaccines, yet choosing not to invest in studies looking at toxicity.

In July 2000, after a full evaluation of the research literature, SafeMinds requested that the FDA immediately recall vaccines containing thimerosal. In the August 16, 2000, response (refusing to conduct a withdrawal), the FDA acknowledged that the agency had never required manufacturers to test the individual components of the vaccines, including the thimerosal. The FDA also stated that only acute toxicity is likely to be found during pre-licensure testing. In 2000, the FDA acknowledged that 'there is no existing guidelines for safe exposure to ethylmercury, the metabolite of thimerosal.' In September 2004, the agency can still not provide a guideline for safe exposure levels for ethylmercury.

It is these types of inconsistencies that have created a level of incredulousness as physicians, scientists, researchers and parents attempt to work with America's leading health related governmental agencies for the protection of children.

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[76] FDA Response to Questions to Dr. William Egan, FDA for the Record of July 18, 2000 hearing before the Government Reform Hearing, US House of Representatives.

[77] CRISP (Computer Retrieval of Information on Scientific Projects) is a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other research institutions. The database, maintained by the Office of Extramural Research at the National Institutes of Health, includes projects funded by the National Institutes of Health (NIH), Substance Abuse and Mental Health Services (SAMHSA), Health Resources and Services Administration (HRSA), Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDCP), Agency for Health Care Research and Quality (AHRQ), and Office of Assistant Secretary of Health (OASH). http://crisp.cit.nih.gov/

One of the leading arguments against the possibility of further restriction on the use of thimerosal is actually the lack of consistent interpretation of the data that is available regarding its safety and efficacy. Mercury, as we have discussed, comes in many forms and potential formulations. While that purports well to the different capacities of the element, it also has caused a quandary regarding safety in those various forms.

The FDA has been aggressive in warning pregnant women and young children to avoid over consumption of mercury-containing fish[78]. *"Research shows that most people's fish consumption does not cause a health concern. However, high levels of mercury in the bloodstream of unborn babies and young children may harm the developing nervous system. With this in mind, FDA and EPA designed an advisory that if followed should keep an individual's mercury consumption below levels that have been shown to cause harm. By following the advisory parents can be confident of reducing their unborn or young child's exposure to the harmful effects of mercury, while at the same time maintaining a healthy diet that includes the nutritional benefits of fish and shellfish."*

The dichotomy of advice from the FDA is at best confusing and at worst a failure to aggressively protect the public once a dangerous mercurial exposure was discovered.

National Institutes of Health

The NIH's efforts to conduct and fund studies evaluating Thimerosal have been at times misdirected and continue to be inadequate given the severity of the potential risk associated with the discovery in 1999 that 8,000 children a day were being exposed to potentially dangerous levels of mercury. (A list of recommended vaccines and their thimerosal content in 1999 is available at Appendix C.) This premier $27 Billion biomedical institution comprised of 26 Institutes and Centers has to date failed to provide evidence to confirm that they have made this matter a priority or that they remain open-minded about the potential that thimerosal in vaccines may be linked to a novel form of autism – mercury-induced autism spectrum disorders.

As the bastion for high quality research, the one study the NIH's National Institute of Allergy and Infectious Diseases (NIAID) notes on in their May 2004 FAQ Public Page on NIAID-funded studies on the subject is the Rochester Study[79] as proof that thimerosal in vaccines is not linked to autism. That the NIAID would fund a small, poorly controlled study and then promote the findings as if it were meeting the gold standards of scientific rigor is highly suspect. The flaws of the study were discussed in a Congressional hearing excerpted below:

[78] http://www.fda.gov/oc/opacom/hottopics/mercury/backgrounder.html

[79] Pichichero ME, Cernichiari E, Lopreiato J, and Treanor J. Mercury concentrations and metabolism in infants receiving vaccines containing thimerosal: a descriptive study. Lancet 360:1737-1741 (2002).

Dr. Weldon. *The Lancet study, only 40 infants. You agree that's much too small a sample size to really make any conclusions?*

Dr. Baskin. *Right. I mean, there are a number of problems with the Lancet studies as I mentioned. But certainly, if the disease occurs in one in 150 children and you only test 40, you may miss that child, very easily miss the child who had the problem, or at best maybe only catch one. Not to mention the other things that have been discussed by several of the panel, the most significant one being they drew the blood much too late. They drew the blood days to weeks later, whereas we know the peak level of methyl mercury----*

Dr. Weldon. *Three to 28 days.*

Dr. Baskin [continuing]. Occur within hours, within 24 hours; yet they drew the blood up to 27 days later. As a matter of fact, to me it's very worrisome. They are still finding some mercury in the blood that far out. It should--you know, you would think it might be gone.

Dr. Weldon. *Is there any----*

Mr. Burton. Would the gentleman yield? Would that be the reason that some families see a very, very rapid change in their children shortly after these vaccinations are given in large numbers? For instance, in our family it was just a matter of a couple days and--boom.

Dr. Baskin. *Correct. All of the data on both methyl and ethyl mercury suggests that the peak level--in other words, the highest level in the blood--is either achieved within hours or at least within 24 hours. So that's--and, again, if it gets in the blood, the blood goes to the brain. We know it has a preferential tendency to be sucked into the brain or to cross into the brain in excess, and so you would expect to see something fairly quickly....*

Dr. Weldon. *Is there any kinetic studies on the clearance of ethyl mercury that are available that could allow you to make conjectures as to what the peak levels might have been based on the blood levels that are available in the Lancet study? Or is that information not known?*

Dr. Baskin. *It's known to a limited extent. There's a study in pre-term infants that received vaccinations. So they--you know, by kind of people not thinking about it, their weight is very small and they receive the same dose, and so it was a very high level. And they looked at some of that data. But, frankly, there is not enough. I think one of the points in the Lancet study is they drew all these complicated curves saying that they knew what the pharmacokinetics were, which refers that they knew how the drug was taken up, how it was absorbed, how it was distributed, but they never caught a peak level. And, of course, you can't even make a comment about pharmacokinetics unless you know the peak level. So, I mean, I think the short answer is there is some--some data available but not enough.* [80]

While discounting the risks of injecting thimerosal into newborns, the NIH has been aggressive in protecting its own. The Campaign for a Mercury Free NIH's website states, "Mercury is a

[80] Vaccines and the Autism Epidemic: Reviewing the Federal Governments Track Record and Charting a Course for the Future, Serial No. 107-153

dangerous, often unrecognized hazard, commonly found at work, home and schools. The Campaign for a Mercury Free NIH seeks to eliminate all unnecessary uses of mercury in the NIH facilities; encourage use of safer alternatives in biomedical research; increase general awareness of mercury hazards; and prevent mercury spills and pollution."[81] How can the NIH scientific community be so aggressive and adamant about reducing their laboratory exposures to mercury, but not take an equally as aggressive stance to protect the nation's children for medical exposures to mercury?

In October of 2003, Clarkson, Magos and Meyers[82] discussed the general issues and various mercurial exposures, including thimerosal, and the relevant hazards associated. This NIEHS/NIH supported effort reviewed many of the current topics of discussion, and quantified part, but not all, of the concerns in today's dialogues.

While Clarkson et al utilized and displayed some of Gossel and Bricker's work,[83] by their own admission, there was much more work to be done.

Clarkson et al repeated Gossel and Bricker's finds that ethyl mercury (thimerosal) has the capacity to attack and injure various neurodevelopment centers. Clarkson et al also review a commonly referred concern of the risk of increased incidence of infectious disease from the population taking an increased decision not to utilize vaccinations for disease prevention. What they failed to state, however, is the integral requirement for an unwavering public trust to the nation's immunization program for such an effort to be successful.

Clarkson et al also admitted that there was a definitive need for additional study to finally study directly thimerosal from all views to settle these questions.

This has been a common request before the NIH and the NIEHS, but to date has not been answered.

All this aside; in their closing remarks, Clarkson et al make a rather definitive statement, "All forms of mercury have adverse effects on health at high doses." We only need to look to the World Health Organization, or the EPA to see the mirror guidelines of 0.1mcg/kg/day. Clarkson et al's effort repeat the findings of the National Academy of Science[84] that America's children were put at risk by exceeding that amounts through pre-natal and post-natal exposures, including through vaccines.

Currently, the Department of Health and Human Services is following the autism research matrix put forth by the National Institutes of Mental Health. The first most telling to the HHS focus and approach to autism in general, is in its design is for repetitive efforts in the short term (and with highest priority) and treatment options, even for overlying biomedical conditions, is not

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[81] http://www.nih.gov/od/ors/ds/index.htm

[82] Thomas W. Clarkson, Ph.D., Laszlo Magos, M.D., and Gary J. Myers, M.D., *The Toxicology of Mercury — Current Exposures and Clinical Manifestations*, N Engl J Med 2003;349:1731-7.

[83] Gossel TA, Bricker JD. Principles of clinical toxicology. 2nd ed. New York: Raven Press, 1990.

[84] Board on Environment Studies and Toxicology. Toxicological effects of methyl mercury. Washington, D.C.: National Research Council, 2000.

scheduled for study until 2013. Also, not found within the HHS document is any address to current treatment research, advancement of biomedical condition treatments to mitigate the suffering of mercury-induced autism victims. Finally, there is no attention provided for family supports.[85]

One criticism to this approach that has been forward is that it is hard to create an appropriate physiologically based treatment focus out of a document that is inherently focused on mental health.

Aside from the challenges of researching autism and its biological issues, is the urgent need to aggressively investigate the actual injury caused by pre- and postnatal exposure to thimerosal and ethylmercury. To date, the NIH response to this remains inadequate.

In reviewing the list of grants funded by NIH since 1972 available on the CRISP Database,[86] SafeMinds learned that 13 studies had been funded between 1999 and 2003 on thimerosal. The studies included several to the University of California, Davis to evaluate the mechanisms of autism and developing an animal model of autism. While several of the funded studies are not related to the toxicity discussion, three studies funded in 2002 and 2003 - one to Marshall University and two funded internally to an NIEHS scientist - should eventually provide further understanding on the effects of thimerosal on the brain. Several of these studies are in press or about to be submitted for publication. A full list of these grants including their abstracts is provided in Appendix D.

The Institute of Medicine Review

In 2001, after calling a public meeting in Boston, the Institute of Medicine Immunization Safety Review Committee (ISRC) issued their first report on the potential link between thimerosal and autism. In this report, the IOM Committee found the hypothesis of a relationship between thimerosal in vaccines and the onset of neurological developmental delays such as autism was biologically plausible. The Committee found a significant lack of scientific data evaluating the safety of thimerosal,[87] but made several direct recommendations for the research necessary to further review and resolve many of the associated questions. A table of those conclusions and recommendations follows:

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[85] Department of Health and Human Services, National Institutes of Health, National Institutes of Mental Health, *Congressional Appropriations Report on the State of Autism Research*, April 2004

[86] CRISP (Computer Retrieval of Information on Scientific Projects) is a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other research institutions. The database, maintained by the Office of Extramural Research at the National Institutes of Health, includes projects funded by the National Institutes of Health (NIH), Substance Abuse and Mental Health Services (SAMHSA), Health Resources and Services Administration (HRSA), Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDCP), Agency for Health Care Research and Quality (AHRQ), and Office of Assistant Secretary of Health (OASH). http://crisp.cit.nih.gov/

[87] Immunization Safety Review: Thimerosal - Containing Vaccines and Neurodevelopmental Disorders (2001) Institute of Medicine

Table 3[88]

CONCLUSIONS

The committee concludes that although the hypothesis that exposure to thimerosal-containing vaccines could be associated with neurodevelopmental disorders is not established and rests on indirect and incomplete information, primarily from analogies with methylmercury and levels of maximum mercury exposure from vaccines given in children, the hypothesis is biologically plausible.

The committee also concludes that the evidence is inadequate to accept or reject a causal relationship between thimerosal exposures from childhood vaccines and the neurodevelopmental disorders of autism, ADHD, and speech or language delay.

PUBLIC HEALTH RESPONSE RECOMMENDATIONS

Policy Review and Analysis

The committee recommends the use of the thimerosal-free DTaP, Hib, hepatitis B vaccines in the United States, despite the fact that there might be remaining supplies of thimerosal-containing vaccine available.

The committee recommends that full consideration be given by appropriate professional societies and government agencies to removing thimerosal from vaccines administered to infants, children, or pregnant women in the United States.

The committee recommends that appropriate professional societies and government agencies review their policies about the non-vaccine biological and pharmaceutical products that contain thimerosal and are used by infants, children, and pregnant women in the United States.

The committee recommends that policy analyses be conducted that will inform these discussions in the future.

The committee recommends a review and assessment of how public health policy decisions are made under uncertainty.

The committee recommends a review of the strategies used to communicate rapid changes in vaccine policy, and it recommends research on how to improve those strategies.

Public Health and Biomedical Research

The committee recommends a diverse public health and biomedical research portfolio.

[88] Immunization Safety Review: Thimerosal - Containing Vaccines and Neurodevelopmental Disorders (2001) Institute of Medicine

Table 3[89] (continued)

Epidemiological Research

The committee recommends case-control studies examining the potential link between neurodevelopmental disorders and thimerosal-containing vaccines.

The committee recommends further analysis of neurodevelopmental disorders in cohorts of children who did not receive thimerosal-containing doses as part of a clinical trial of DTaP vaccine.

The committee recommends conducting epidemiological studies that compare the incidence and prevalence of neurodevelopmental disorders before and after the removal of thimerosal from vaccines.

The committee recommends an increased effort to identify the primary sources and levels of prenatal and postnatal background exposure to thimerosal (e.g., Rho (D) Immune Globulin) and other forms of mercury (e.g., maternal consumption of fish) in infants, children, and pregnant women.

Clinical Research

The committee recommends research on how children, including those diagnosed with neurodevelopmental disorders, metabolize and excrete metals—particularly mercury.

The committee recommends continued research on theoretical modeling of ethylmercury exposures, including the incremental burden of thimerosal with background mercury exposure from other sources.

The committee recommends careful, rigorous, and scientific investigations of chelation when used in children with neurodevelopmental disorders, especially autism.

Basic Science Research

The committee recommends research to identify a safe, effective, and inexpensive alternative to thimerosal for countries that decide they need to switch from using thimerosal as a preservative.

The committee recommends research in appropriate animal models on the neurodevelopmental effects of ethylmercury.

The IOM conclusions from 2001 (as noted in Table 3) admitted to the lack of specific study and data necessary for accomplishing the task of allowing a full scientific review to the issues. Subsequently, there appears to have been selective adaptations of their conclusions and recommendations leading to its final report.

[89] Immunization Safety Review: Thimerosal - Containing Vaccines and Neurodevelopmental Disorders (2001) Institute of Medicine

First, in its "Public Health Response Recommendations", the committee's suggestion for exclusive use of thimerosal free vaccines "despite the fact there might be remaining supplies of thimerosal-containing vaccine available"[90] was never fully realized nor implemented. Rather, a slow transition began, with patchwork efforts to move through to the goal of exclusive use of thimerosal-free vaccines. Today, there is still readily available and utilized thimerosal-containing stock in our immunization programs supplies.

Second, there was never a full dialogue provided to the IOM's fifth Public Health Response recommendation, "a review and assessment of how public health policy decisions are made under uncertainty."[91] Rather, a perceived waiting game began pending a final report by the Immunization Safety Review Committee (ISRC).

Regarding the ISRC's epidemiological studies recommendations, only half were fully accomplished in the years between initial and final reports. Neither the case-control nor clinical trial studies were ever accomplished, providing only a partial body of their stated needs prior to the issuing of the final report.

The largest failing in research falls from the clinical and basic science realms. Fully, none of the five recommended, and requisite for conclusion, studies were fulfilled. While there has been discussions and postulates (i.e. Aposhian[92]), research into the arena of excretion and the potential of efflux disorder (i.e. Wilson's Disease) has never been fully accomplished. Theoretical modeling of mercury burden levels, with reference to thimerosal, has primarily been found accomplished through private sector efforts, as has the use of various forms[93] of chelation therapy and their application in the mercury-injured autism population To date, there has been no formalization or recommendation for alternative preservative use, nor has there been public resources pledged or provided for attempting to locate thimerosal alternatives.

Finally (with regard to the ISRC initial report conclusions and recommendations) while some appropriate animal modeling has been accomplished, such as Hornig et al[94], this area of study has not been fully supported through public resources with the enthusiasm suggested by the ISRC report as necessary to the discussion.

In review, with respect to the initial IOM report, nine of the sixteen (56%) ISRC recommendations for public health response or research cannot be considered accomplished or fulfilled to the degree purported as necessary within that report. This pattern of HHS's contracting with the NAS/IOM to conduct vaccine safety evaluations and receive advice which they fail to adopt is a long-standing failure within the department. In 1991 and 1994, IOM provided evaluations of existing scientific evidence connecting vaccines and the onset of a

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[90] Immunization Safety Review: Thimerosal - Containing Vaccines and Neurodevelopmental Disorders (2001) Institute of Medicine

[91] Immunization Safety Review: Thimerosal - Containing Vaccines and Neurodevelopmental Disorders (2001) Institute of Medicine

[92] "*A Toxicologist View of Thimerosal and Autism*", H. Vasken Aposhian, presentation before the IOM-ISRC meeting #9, 9 February 2004

[93] Oral, topical, transdermal, and IV chelating treatments

[94] *Neurotoxic effects of postnatal thimerosal are mouse strain dependent*, M Hornig, D Chian and W I Lipkin

number of conditions. At each review the IOM pointed out significant gaps in the science; however, in the years that followed, most of the advice was ignored.

It was the National Academy of Sciences that confirmed the EPA's lower limit on methylmercury as being scientifically valid in the late 1999. When the FDA began looking at the level of exposure to thimerosal in vaccines, there was an assumption that in their absence of pharmacokinetic data on thimerosal that ethyl mercury was as at least as toxic as methylmercury.

It is important to remember that according to Neal A. Halsey, MD, Institute of Vaccine Safety, Johns Hopkins University and long time advisor to FDA and CDC, that he and other advisors missed the increasing exposure to mercury in the thimerosal because the thimerosal content was presented on the label as 0.01% rather than 25 mcg.[95]

The most recent IOM meeting (9 February 2004) focused on whether ethyl mercury is potentially safer than methyl mercury, which is a known biotoxin. This most recent of a (to date) total of nine meetings on the subject of vaccines and autism again showed a division some within the scientific and medical communities have regarding these issues.[96] It was noteworthy that the IOM-ISRC narrowed their focus of their deliberation as to whether there was a Thimerosal-Autism Spectrum Disorder link rather than the original and interim Thimerosal-Neurodevelopmental Disorder link. In doing so, the ISRC disallowed discussion and debate of several studies, including the various versions of Verstraeten et al's efforts.[97]

When notice of this scheduled to be the "final" meeting, was posted, there were numerous calls for postponement. Researchers, research groups, and members of Congress all submitted requests to the IOM for the meeting to be postponed as there were (at minimum) two known studies completing their research and preparing for publishing. These studies, a National Institute of Allergy and Infectious Diseases effort by Polly Sager, Ph.D[98], and a Columbia Medical School effort, *Neurotoxic effects of postnatal thimerosal are mouse strain dependent*[99] by Hornig et al were unfortunately presented in incomplete form.

It was unfortunate that the IOM did not heed the multiple cause for delaying this meeting as the results of these two key studies would go on to directly contradict the findings of the soon to be published IOM-ISRC report.

The majority of presenters at this meeting felt that there was a clear link between vaccines, specifically thimerosal/mercury containing vaccines, and Autism Spectrum Disorders. Only a small minority felt that there was either no or only a slight potential for harm from mercury.[100]

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[95] *Commentary on Potential Risk from Thimerosal for Infants*, presentation to the IOM-ISRC, July 16, 2001, Cambridge, MA by Neal A. Halsey, MD, Institute of Vaccine Safety, Johns Hopkins University

[96] http://www.iom.edu/subpage.asp?id=18065

[97] Thimerosal VSD Study – Phase 1, Update 2/29/00, Thomas Vertraeten, Robert Davis, Frank Destefano, obtained via FOIA by SafeMinds, Summer 2001

[98] NIAID Studies on Thimerosal, Sager et al, NIAID, NIH, DHHS, presentation to the IOM, February 9, 2004

[99] Hornig, Chian, Lipkin, Molecular Psychiatry (2004), 1–13, *Neurotoxic effects of postnatal thimerosal are mouse strain dependent*

[100] http://www.iom.edu/subpage.asp?id=18065

What is known, if only reviewed separately, is mercury is a known toxin, specifically a known neurotoxin with a high capacity to permanently injure and/or cause developmental arrest.[101]

In early May 2004 the IOM website makes the following statement:

> *The evidence reviewed at the time neither proves nor disproves the hypothesis that thimerosal-containing vaccines could cause neurodevelopmental disorders, such as autism or attention deficit-hyperactivity disorder. The IOM will review newly released data on vaccines and autism in early 2004.*[102]

In their May 2004 report[103] the IOM-ISRC actually utilizes the lack of relevant science recommended in its initial report as a foundation stone to its current conclusions. In its recommendations for policy review, the ISRC cites a "lack of direct evidence for a biological mechanism" in its tendency to now discount any thimerosal-autism link. An understanding of the language here is crucial. It was not for completed studies affording no such evidence that this statement is forwarded, rather that there was never adequate resources committed for the accomplishing of such studies, and therefore, no evidence.

The ISRC further stated its reaffirmation to its previous recommendation to conduct clinical and epidemiological studies "of sufficient rigor...to better understand genetic or environmental causes of ASD."[104] The ISRC did not, however, acknowledge the failure to have these matters accomplished in the intervening years.

In truth, many of the general epidemiology and research recommendations of the 2004 report are recitations of the original reports recommendations, without acknowledgement to the lack of Public Health Service accomplishment as previously put forth.

In its "Clinical Studies" recommendations, while the ISRC recognizes the utilization of chelation as a popular therapy for the treatment of ASD, it points to a lack of accepted scientific standards evidence (double blind studies, etc.) providing chelation as an appropriate therapy for ASD. The IRSC's failure to support the necessary and recommended research looking at therapeutic interventions for mercury fails this community.

Additionally, the manner in which the IOM's committee addresses these recommendations regarding chelation therapy for ASD treatment again highlights the ISRC's lack of understanding of the issues. Co-morbid diagnoses of heavy metal, including mercury, toxicity is often noted with ASD or NDD diagnosed children. The chelation therapies are therefore appropriately ascribed and prescribed for the treatment of those heavy metal toxicities, not the ASD or NDD *per se*. That evidences of post chelation improvement in the patient's ASD or NDD condition should have been seen as a path deserving further rigorous research, rather than one to discard.

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[101] Zh Mikrobiol Epidemiol Immunobiol 1983 Mar;(3):87-92

[102] http://www.iom.edu/focuson.asp?id=4189

[103] Immunization Safety Review: Vaccines and Autism (2004), Institute of Medicine

[104] Immunization Safety Review: Vaccines and Autism (2004), Institute of Medicine

The 2004 IOM report also fails to reprimand HHS for its fulfill any of the IOM's other recommendations for clinical or basic science research it had previously deemed requisite to a full and adequate review of the issue. This is not surprising, however; given that the IOM first requested that HHS evaluate possible connections between autism and vaccine injury in 1991. A recommendation that was ignored: *"...no evidence bearing on a causal relation between DPT vaccine and autism... In the course of its review, the committee encountered many gaps and limitations in knowledge bearing directly and indirectly on the safety of vaccines. These include inadequate understanding of the biologic mechanisms underlying adverse events following natural infection or immunization, insufficient or inconsistent information from case reports and case series, inadequate size or length of follow-up of many population-based epidemiologic studies, and limited capacity of existing surveillance systems of vaccine injury to provide persuasive evidence of causation. The committee found few experimental studies published in relation to the number of epidemiologic studies published. Clearly, if research capacity and accomplishment in these areas are not improved, future reviews of vaccine safety will be similarly handicapped."*[105]

Table 4.1[106]

Charting Institute of Medicine - Immunization Safety Review Committee Recommendations
Research Deemed Necessary to Adequately Review Potential Causality Between Thimerosal and Neurodevelopmental Disorders
From 2001 Report to 2004 Final report

	Epidemiology Research		
Recommendation	Funded	Accomplished	Other/Notes:
"case-control studies examining the potential link between neurodevelopmental disorders and thimerosal-containing vaccines"	NO	NO	
"further analysis of neurodevelopmental disorders in cohorts of children who did not receive thimerosal-containing doses as part of a clinical trial of DTaP vaccine"	NO	NO	
"compare the incidence and prevalence of neurodevelopmental disorders before and after the removal of thimerosal from vaccines"	YES Statens Serum Institut*	YES Statens Serum Institut*	Hviid et al – does not conclude differences in (specifically) Denmark's pre- and post-thimerosal exposure eras data**

[105] Adverse Effects of Pertussis and Rubella Vaccines (1991) Institute of Medicine
[106] Recommendation quotes as taken from: Immunization Safety Review: Thimerosal - Containing Vaccines and Neurodevelopmental Disorders (2001) Institute of Medicine

Table 4.1[107] (continued)

"identify the primary sources and levels of prenatal and postnatal background exposure to thimerosal (e.g., Rho (D) Immune Globulin) and other forms of mercury"	NO	NO

* Conflicts of interest noted in study as Statens Serum Institut (State Serum Institute) – Denmark, is that nation's leading vaccine manufacturer as well as research institute.
** Thimerosal exposure levels and autism rates differed from United States

Table 4.2[108]

Clinical Research

Recommendation	Funded	Accomplished	Other/Notes:
"research on how children, including those diagnosed with neurodevelopmental disorders, metabolize and excrete metals—particularly mercury"	YES ATSDR	YES University of Rochester	Clarkson et al - Information not presented nor made public. FOIA request pending.
"continued research on theoretical modeling of ethylmercury exposures, including the incremental burden of thimerosal with background mercury exposure from other sources"	YES (Partial) SafeMinds	Partial	Postnatal exposures reviewed and presented to IOM. Requests to fund prenatal exposure modeling have gone unanswered.
"careful, rigorous, and scientific investigations of chelation when used in children with neurodevelopmental disorders, especially autism"	NO	NO	While EDTA chelation is and remains an approved therapy for meavy metal toxicities, no requests for federal funding for use in alternative therapies has yet been approved

[107] Recommendation quotes as taken from: Immunization Safety Review: Thimerosal - Containing Vaccines and Neurodevelopmental Disorders (2001) Institute of Medicine
[108] Recommendation quotes as taken from: Immunization Safety Review: Thimerosal - Containing Vaccines and Neurodevelopmental Disorders (2001) Institute of Medicine

Table 4.3[109]

	Basic Science Research		
Recommendation	Funded	Accomplished	Other/Notes:
"identify a safe, effective, and inexpensive alternative to thimerosal for countries that decide they need to switch from using thimerosal as a preservative"	NO	NO	
"research in appropriate animal models on the neurodevelopmental effects of ethylmercury"	YES NIAID NIEHS	Washington University	Burbacher et al – differences between ethylmercury and methylmercury noted. EtHg bonds stronger and is more neurotoxic. Requests for funding to further findings and research: DENIED
	YES (Private) SafeMinds & MIND Institute at UC Davis	Columbia University	Hornig et al – Found NDD/autism response to administration of vaccine level amounts of thimerosal in genetically susceptible mice

This latest report apparently puts forth as best policy and practice a recommendation for continued "surveillance of ASD as exposure to thimerosal declines." This strategy, however, will not prove effective as more and more thimerosal-containing vaccines are "recommended", and therefore frequently administered, but are not formally on the pediatric schedule.

As some of the (here included) scientific efforts report, there is an apparent genetic susceptibility component to the Thimerosal-Autism link, such a reactive posturing (post event surveillance) will not prove beneficial to those who may be injured in any interim.

In November 2003, the Department of Health and Human Services, National Institutes of Health, National Institute of Mental Health participated in a Congressionally mandated "Autism Summit" in Washington, DC. One of the primary purposes of this conference was to allow the presentation of an Interagency Autism Coordinating Committee (IACC) research matrix providing the roadmap for focus and funding for related NIH expenditures. Again, this event provided insight to an interagency prejudice to the mercury-autism hypotheses. Minimal discussion or resources were scheduled to be provided in the (now published) IACC Autism Research Matrix[110], and the agencies surrounding report minimized or dismissed the hypotheses.

Several research and parent groups spoke out to the IACC's matrix lack of focus for resources to the mercury-autism issue, but were summarily discounted and no modification to the research matrix was provided.

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[109] Recommendation quotes as taken from: Immunization Safety Review: Thimerosal - Containing Vaccines and Neurodevelopmental Disorders (2001) Institute of Medicine

110 http://www.nimh.nih.gov/autismiacc/CongApprCommRep.pdf

The Science: An Update and New Findings

While the debate focuses upon mercury laden medical products, one issue that needs most to be resolved is the inefficiency in science to have accurately qualified the efficacy and safety of thimerosal.

It would appear that many foreign researchers were ahead of the curve when compared to recognition in the United States to the hazards of thimerosal exposure. As early as 1977, Russian researchers began recognizing the potential health hazards from ethyl mercury exposures.[111] Additional studies conducted through the 1980s also documented toxic results from the utilization of thimerosal in various preparations and vaccines.[112,113,114]

The most current and recently presented research (reviewed within) has primarily focused upon two areas of the debate. The first is the epidemiological standing with relation between mercury and neurodevelopmental disorders. The second is the beginnings of understanding the human response to ethyl-mercury and why it is not a constant.

Boyd Haley, PhD, professor and chair at the University of Kentucky, Department of Chemistry has given great insights to the neurotoxic effects and blood/brain transport pathways of ethyl mercury. In his 2001[115] presentation to the IOM-ISRC, Dr. Haley provided three clear and specific conclusions from his research:

- Thimerosal is the major toxic component of most vaccines
- Thimerosal is a more potent inhibitor of many metabolic enzymes than is mercuric chloride
- Due to synergistic toxicity, thimerosal exposure through vaccines with aluminum should be considered quite capable of causing severe neurological and systemic damage.

In 2004, Dr. Haley provided further evidence to the IOM-ISRC regarding the toxicity of ethyl mercury (thimerosal).[116] In that discussion, Haley provided additional insights to several questions being raised regarding exposure vs. injury, and why there appeared to not be a static relationship between the two.

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111 Late After Effects of the Nervous System Pathology Provoked by the Action of Low Ethyl-Mercuric-Chloride Concentrations, Mukhtarova, 1977

112 Evaluation of the toxic action of prophylactic and therapeutic preparations on cell cultures of different types and origin. – II, Kravchenko et al - 1982

113 Evaluation of the toxic action of prophylactic and therapeutic preparations on cell cultures of different types and origin. – III, Kravchenko et al - 1983

114 Cytotoxic action of the chemical substances found as admixtures in medical immunobiological preparations, Chervonskaia et al - 1988

[115] Haley, Boyd E., *Mercury Toxicity and Its Relationship to Neurological Disease*, Presentation to the Institute of Medicine, Immunization Safety Review Committee, 16 July 2001

[116] Haley, Boyd E., *Mercury Toxicity: Genetic Susceptibility and Synergistic Effects*, Presentation to the Institute of Medicine, Immunization Safety Review Committee, 9 February 2004

Dr. Haley provided insights to these matters, which may be best summed up through his presented conclusions from that meeting: [117]

- There appears to be a subset of the population that cannot effectively excrete mercury and are at a greater risk to exposures to mercury than are the general population. Genetic susceptibility is critical.
- Presence of other heavy metals, antibiotics, etc. may enhance the toxicity of thimerosal. Synergistic toxicities must be considered.
- Estrogen decreases thimerosal toxicity whereas testosterone increases the toxicity. Gender effects are involved.

A review to the potential issue of increased incidence versus diagnostics (or diagnostic substitutions) was completed by Croen et al[118] as a follow up to another Croen et al[119] effort a year prior. During this data review, Croen et al hypothesized that there was not a true "increase" in the incidence in autism, but rather that there were a combination of better diagnostics, and the diagnostic substitution of patients which would put forth such a prediction.

In their effort, Croen et al stated their effort demonstrated "that over 100% of the increase in autism from 1987-1994 is an artifact of changes in diagnostic practices."[120] In Blaxill et al's review[121] of Croen's effort, however, several errors were found in calculations within the data sets, which created this false (Croen's) impression. In their conclusions, Blaxill et al did put forth one telling statement, that in the end, Autism research is under funded when compared to "disorders with a much lower incidence in the population."[122]

Following Blaxill et al's review, Croen and Grether reviewed their data, hypothesis and conclusions. After careful consideration, Croen and Grether published their response[123] to Blaxill, in which the admit that the reclassification did not play an integral role to the increases in autism prevalence; that they had underacertained and incorrectly calculated the autism rates; and withdrew their (now proved flawed) study.

Inexplicably, those looking to dismiss the Thimerosal-NDD/autism link still frequently cite Croen's original effort in support of their argument, disregarding the authors' own refutation of their original finds.

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[117] Haley, Boyd E., *Mercury Toxicity: Genetic Susceptibility and Synergistic Effects*, Presentation to the Institute of Medicine, Immunization Safety Review Committee, 9 February 2004

[118] Croen, Grether, Hoogstrate and Selvin, 2002

[119] Croen, Grether and Selvin, 2001

[120] Commentary: Blaxill, Baskin, and Spitzer on Croen *et al.* (2002), The Changing Prevalence of Autism in California

[121] Commentary: Blaxill, Baskin, and Spitzer on Croen *et al.* (2002), The Changing Prevalence of Autism in California

[122] Commentary: Blaxill, Baskin, and Spitzer on Croen *et al.* (2002), The Changing Prevalence of Autism in California

[123] *A Response to Blaxill, Baskin, and Spitzer on Croen et al. (2002), "The Changing Prevalence of Autism in California*, Journal of Autism and Developmental Disorders, Vol. 33, No. 2, April 2003

In 2003, Holmes et al[124] began to fortify today's roots regarding the epidemiological issues surrounding ethyl mercury and its potential to induce neurodevelopmental disorders. In this effort, the hairs from babies' first cuts were reviewed for levels of mercury for gestational maternal-fetal exposure through immunoglobulin and maternal amalgams. This first of its kind study actually had several instructive findings. The most enlightening result was the lower overall rate of (excreted) mercury in the infants' hair for children diagnosed with autism. This finding strongly supported the widely accepted hypothesis connecting autistic children's inability for excreting mercury, and as a precursor to mercury induced neurotoxicity and subsequent development disorders.

Non-autistic children were found to have substantially higher mercury levels in their first cuts, purporting that their excretion capacity for mercury is less hindered, at least in comparison to the capacity of autistic children.

Redwood et al put forth in 2001 an effort entitled *"Predicted Mercury Concentrations in Hair From Infant Immunizations: Cause for Concern" (NeuroToxicology 69-2001)*[125] This precursor to Holmes et al's efforts laid well the original modeling for taking the premise of predicted mercury levels and the corollary to mercury toxicity. These two bodies have solidified the premise that many children have some measure of an efflux disorder, and the subsequent maintained blood levels of mercury, combined with their opportunity to cross the blood brain barrier, move to create a neurotoxic atmosphere and subsequent developmental injury.

Holmes et al served to confirm further the findings of Redwood, and began to provide further insights and quantification of the excretion disorder premise. As there is little debate about the neurotoxicity of mercury, rather the discussion needed to be shifted to why this matter was not a constant in society with a 1:1 ratio of mercury exposure to developmental neurotoxicity.

One of the greatest recent quantifications of these issues occurred at the National Academies of Science, Institutes of Medicine, ninth meeting of the Immunization Safety Review Committee (09 February 2004). Here, H. Vasken Aposhian, Ph.D. provided a toxicologist's view[126] to the matter, integrating many of the themes from Holmes and Redwood.

Aposhian reviewed the issue of mercury toxicity in all of its forms, and did not choose to single out the thimerosal issue specifically. Rather, he put forth the necessity to recognize all of the potentials for mercury exposure, including environmental, to appropriately qualify the disease process first, then allow appropriate insight to the processes leading to injury.

Following the reviews of routes for exposure, Aposhian began by putting forth the question many had been postulating, "Is autism an efflux disorder?"[127] A presentation was then provided

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[124] Reduced Levels of Mercury in First Baby Haircuts of Autistic Children, International Journal of Toxicology, 22:277–285, 2003

[125] *Predicted Mercury Concentrations in Hair From Infant Immunizations: Cause for Concern (NeuroToxicology 69-2001*

[126] Immunization Safety Review: Meeting 9: Aposhian Presentation, http://www.iom.edu/includes/dbfile.asp?id=18390

[127] Immunization Safety Review: Meeting 9: Aposhian Presentation, http://www.iom.edu/includes/dbfile.asp?id=18390 - Slide 7

to the potential similarities between in structure and process between mercury induced neurodevelopmental disorders, with specificity to autism, and Wilson's Disease.[128]

Aposhian's utilization of Wilson's Disease as a model of an efflux disease showed a clear parallel involving a toxic metal exposure, a supportively genetic susceptibility, and accumulation to toxicity, and relevant organ and central nervous system signs and symptoms.[129] Here we begin to transition from the postulatory review of the mercury-induced neuro-injury, and into the realm of recognizing defined models for similar occurrences with other neurotoxic metals, such as mercury.

Aposhian refers to Holmes et al and Bradstreet et al[130] as a basis (to this cited presentation[131]) for recognition of the increased mercury burden typically found in autistic children, and the appearance to provide a lack of an effective mercury efflux system to address any cumulative exposure, let alone the burden created from vaccines.

While Aposhian puts forth the suspect parallel regarding an efflux disorder related mercury induced autism, he puts forth two postulates as to the routes for response to thimerosal creating the final symptom, however, both reside in the recognition of a basic genetically disposed efflux failure.

The first postulate is that there is an efflux impairment to which thimerosal is introduced into an unfavourable environment. Thimerosal would then be a final insult or "trigger" leading to autism.[132]

The second postulate additionally relies on the efflux impairment, but provides that the thimerosal introduction simply provides an increased mercury burden in the child. This postulate provides that the thimerosal exacerbates pre and post expected environmental exposure, putting the mercury burden over the threshold to neurotoxicity.

While admitting a need for, and providing a call for, additional relevant research to better track which of the two postulates leads to the final insult, there is little room for questioning the route to injury relevance of Aposhian's presentation.

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[128] "Wilson's disease is an inherited disorder in which excessive amounts of copper accumulate in the body. Although the accumulation of copper begins at birth, symptoms of the disorder appear later in life, between the ages of 6 and 40. The primary consequence for approximately 40 percent of patients with Wilson's is liver disease. In other patients the first symptoms are either neurological or psychiatric or both, and include tremor, rigidity, drooling, difficulty with speech, abrupt personality change, grossly inappropriate behavior and unexplicable deterioration of school work, neurosis or psychosis." Excerpted from National Institutes of Health via http://www.ninds.nih.gov/health_and_medical/disorders/wilsons_doc.htm

[129] Immunization Safety Review: Meeting 9: Aposhian Presentation, http://www.iom.edu/includes/dbfile.asp?id=18390 - Slide 8

[130] Jeff Bradstreet et al, *A Case-Control Study of Mercury Burden in Children with Autism Spectrum Disorders*

[131] Immunization Safety Review: Meeting 9: Aposhian Presentation

[132] Immunization Safety Review: Meeting 9: Aposhian Presentation, http://www.iom.edu/includes/dbfile.asp?id=18390 - Slide 16

Supportive to Aposhian's presentation were findings that "thimerosal pharmacokinetics obtained using non-autistic children are not the same as those expected for autistic children."[133] This furthered not only the issue of an efflux disorder, but to the variance in kinetics involved.

Aposhian also cautioned the amount of effort and focus being placed upon the issue of epidemiology surrounding mercury induced neurotoxicity. His statement was simple, "Epidemiological studies cannot prove cause and effect. Rather, they reveal statistical correlations."[134]

In following this statement, Aposhian explained the myriad issues and variables concerning a simple reliance upon epidemiological studies when trying to locate the root issues to injury. He also provided a lack of parallel guidance and support for further toxicological and other studies were not allowing for an accurate view of the matter. This especially in light of recognized and questioning of dilution of data sets seen in many epidemiological studies, which have led to much of the debate.

In the end, Aposhian put forth that from a toxicological perspective, the link between mercury, with specific mention to thimerosal, is strong and supportive to injury through a mercury efflux disorder.[135]

At the ninth Immunization Safety Review meeting at the Institutes of Medicine (09 February, 2004), Jeff Bradstreet, MD, FAAFP presented a culmination of efforts which brought much of the within described material into a new light, including genomics.

In his presentation, Bradstreet brought forth two efforts regarding thimerosal induced neurodevelopmental injuries. His first body of work, *"A Case-Control Study of Mercury Burden in Children with Autistic Spectrum Disorders"*[136] reviewed much of the debate regarding the Autism epidemic and the linear association with the increased use of thimerosal containing pediatric vaccines. Next, this similarly walked through a case control study examining the specifics of mercury body burdens consistently found in autistic children post chelation, and the potential for it to purport to some measure of an efflux disorder allowing for maintenance of excess mercury in the affected children.

Bradstreet et al also expresses and includes reference the epidemiological data link between increased childhood vaccines and childhood neurodevelopmental disorders.

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[133] Immunization Safety Review: Meeting 9: Aposhian Presentation, http://www.iom.edu/includes/dbfile.asp?id=18390 - Slide 18

[134] Immunization Safety Review: Meeting 9: Aposhian Presentation, http://www.iom.edu/includes/dbfile.asp?id=18390 - Slide 20

[135] Immunization Safety Review: Meeting 9: Aposhian Presentation

[136] Bradtreet et al, *"A Case-Control Study of Mercury Burden in Children with Autistic Spectrum Disorders"* Journal of American Physicians and Surgeons, Volume 8, Number 3, Summer 2003

This 2003 effort continues to follow the same path that Bernard et al,[137] Blaxill et al,[138] Holmes et al,[139] Redwood et al,[140] and Aposhian, Ph.D.,[141] with each step building the foundation of understanding and facts behind the predecessor's premise. Bradstreet's latest collaboration (Bradstreet, Wakefield and James)[142] has taken the previous views and initiated the pathophysiological links. In his Institute of Medicine presentation,[143] "Biological Evidence of Significant Vaccine Related Side-effects Resulting in Neurodevelopmental Disorders", Bradstreet again reviewed the foundational and current efforts drawing the direct linear corollary between mercury exposure through vaccines and increased autism in the United States.

Bradstreet took a holistic view to the issues, including the relevant timing from birth to vaccination to recognized deficit(s) to diagnosed injury. Looking at epidemiological studies relevant to the issue, this should have been enough to create a want for erring on the side of caution pending further and open study.

Next, Bradstreet showed historic cases,[144] historic cautions,[145] and historic patterns of high mercurial (thimerosal) exposures,[146] and the historic policies (yet effected) from the WHO, EPA and CDC regarding "acceptable" mercury exposure levels, and the excesses created through the pediatric vaccination programs.

It was not until the genomics review was accomplished that one can now begin to see why the vaccination to injury ratio is not 1:1. Rather, Bradstreet reported that the most recent efforts have found a genomic susceptibility which inhibits certain exposed children's ability to appropriately excrete the mercury.

A single recognized nucleotide polymorphism found in children with autism spectrum disorders provides the mapping from exposure to injury. Specifically, SNP's inhibited by thimerosal involving methylation and sulfation disallow a "normal process" for mercurial excretion. This event creates and maintains the elevated mercury body burden, which provides for the neurotoxic atmosphere, thus providing the architecture for neurodevelopmental injury resulting in injuries such as autism spectrum disorders.

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[137] Bernard et al, *Autism: A unique type of mercury poisoning*, April 3, 2000

[138] Commentary: Blaxill, Baskin, and Spitzer on Croen *et al.* (2002), The Changing Prevalence of Autism in California

[139] Reduced Levels of Mercury in First Baby Haircuts of Autistic Children, International Journal of Toxicology, 22:277–285, 2003

[140] *Predicted Mercury Concentrations in Hair From Infant Immunizations: Cause for Concern (NeuroToxicology 69-2001*

[141] Immunization Safety Review: Meeting 9: Aposhian Presentation, http://www.iom.edu/includes/dbfile.asp?id=18390

[142] Jeff Bradstreet, MD, FAACP; Andrew Wakefield, MB, BS, FRCS, FRCPath; S. Jill James, Ph.D.

[143] Immunization Safety Review: Meeting 9: Aposhian Presentation, http://www.iom.edu/includes/dbfile.asp?id=18578

[144] Cinca et al, *Accidental ethyl mercury poisoning with nervous system, skeletal muscle, and myocardium injury*, J Neuron Neurosurg Psychiatry, 1980, Feb;43(2):143-9

[145] Fagan et al, *Organ mercury levels in infants with omphaloceles treated with organic mercurial antiseptic*, Archives of Diseases in Children, 1977, 52, 962-964

[146] Stajich et al, *Iatrogenic exposure to mercury after Hepatitis B vaccination in preterm infants*, J Pediatr 2000;136;679-81)

What Bradstreet, Wakefield and James have accomplished is the initial recognition and mapping to the trigger mechanism(s) involved between the thimerosal (mercury) exposure and the end stage resultant disease. In reviewing the history of research regarding this issue, like so many other medical finds, its been a process of reverse engineering. First was the recognition of the epidemic; next the suggested likeness between mercury poisoning and autism spectrum disorders; then the potential ties discovered through efforts in epidemiology; and now the causal trigger mechanism/event.

A recent publishing in Molecular Psychiatry by Deth et al,[147] furthers the scientific understanding of mercury/thimerosal potential influence in pre- and post-natal development. Quoting from Deth's abstract, "Neurodevelopment toxins, such as ethanol and heavy metals [thimerosal], interrupt growth factor signaling, raising the possibility that they might exert adverse effects on methylation." The basic results of this "adverse effect" are expressed in Deth's statement, "Our findings outline a novel growth factor signaling pathway that regulates MS activity and thereby modulates methylation reactions, including DNA methylation. The potent inhibition of this pathway by ethanol, lead, mercury, aluminum and thimerosal suggests that it may be an important target of neurodevelopmental toxins."

What Deth et al are continuing is a the building of the path to understanding of the role thimerosal plays in interruption of various developmental processes which lead to neurological development disorders, including autism.

In response to animal modeling/testing needs for furthering the understanding between thimerosal and NDD, two recent studies have been concluded. First, is Burbacher et al's effort reviewing mercury blood levels in primates exposed to vaccine levels of methyl mercury exposure.[148] While the initial presentation provides that there are clear differences between ethyl and methyl mercury in blood levels over time, additional insights through this study have provided that ethyl mercury has a stronger bond than methyl mercury and is more neurotoxic.

This project, funded by NIAID, has forwarded nearly as many questions as it has answered. Specifically, while the mercury/blood level modeling has been mapped, the true levels, and increased propensity, for ethyl mercury to cross, and potentially to remain past, the blood-brain barrier.

A request by the researchers to fund further study this issue, given the findings promoting caution to the use of ethyl mercury (thimerosal), has to date gone unfulfilled, and may need to be accomplished privately to provide further answers.

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[147] M Waly, H Olteanu, R Banerjee, S-W Choi, J B Mason, B S Parker, S Sukumar, S Shim, A Sharma, J M Benzecry, V-A Power-Charnitsky and R C Deth "*Activation of methionine synthase by insulin-like growth factor-1 and dopamine: a target for neurodevelopmental toxins and thimerosal*", Molecular Psychiatry, April 2004, Volume 9, Number 4, Pages 358-370

[148] Burbacher, Shen, Clarkson, "Comparative Toxicokenetics of Methyl mercury and Thimerosal in Infant *Macca fasicularis*" presentation to Institute of Medicine, Immunization Safety Review Committee, 9 February 2004

The next recently released study is from the Mailman School of Public Health at Columbia University. In this study,[149] Hornig et al looked at the effects of vaccine level thimerosal exposure on mice with a specific genetic susceptibility. This research postulate was created following the increasing body of scientific evidence promoting that the Thimerosal-NDD link is predicated upon certain genetic predispositions/genomic defects, which refer to autoimmune disease sensitivity.

Hornig et al found that the selected mice universally showed an implication of "genetic influences" that led to responses and activities that mimic those found in Autism Spectrum Disorders (including growth retardation, hypoactivity, social withdrawal, gross motor coordination, repetitive motions/movements, confusion or dissociation with familiar surrounds, and other dysfunctional behaviours.)

Hornig et al's research also found physiological effects relevant to the brain and cranium in the creation of abnormalities resultant from vaccine level thimerosal exposure.

What all of the arena's researchers, regardless of position, are in agreement to is the need for additional research to follow these matters through, for better understanding, potential treatments, and establishing policies and practices which will reverse the current epidemic trend.

With support found for the additional research comes the additional burden to assure the honesty and accuracy of the findings, and to assure that every measure is taken to provide all of the answers to all of the questions.

Conclusions and Recommendations

There needs to be several efforts put forth, and universally supported, to maintain the highest level of protection for our children.

In the 1960's and 1970's, seat belt regulation and legislation began being introduced, not because of the known fact that they would save lives and prevent injury, but because research showed that there were strong links between seat belt use, and injury or death prevention.

Soon, safety glass was introduced, and mandated through regulation for use in most automobile applications. This was actually not done secondary to excessive research and awareness of the dangers of non-laminate glass, but due to a body of anecdotal evidence that convinced legislators and regulators to make the necessary changes.

Both of these actions were predicted to decimate the automobile industry, as the extra costs incurred would ruin manufacturer profits, and create a consumer price increase that would push automobiles out of the budget of most Americans. The decisions taken then were driven on a single point, "if it saves one life."

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[149] Hornig, Chian, Lipkin, Molecular Psychiatry (2004), 1–13, *Neurotoxic effects of postnatal thimerosal are mouse strain dependent*

Of course, we realize today that none of these negative predictions came to fruition, and set a course for constant review and upgrading for any and every safety related device relevant to the automobile industry. Even proven designs are constantly reviewed from an adversarial position to make sure that the decisions taken even months previously are grounded with constant scientific review.

Thimerosal has been utilized since the 1930's. During the subsequent seven-plus decades, there has been no formal review of its safety and efficacy, especially in pediatric vaccines. To date, HHS has failed to provide even one comprehensive pharmacokinetic study to the Congress or the American public. Had this foundational research been required of manufacturers prior to its introduction into the vaccine supply, much harm may have been prevented.

The matter of thimerosal inclusion in vaccines is one area where our response does not fit our normal paradigm for looking into any areas of safety, whether automobile manufacturing or medication/vaccine.

In nearly all other areas of regulation, or effective legislation, Americans have consistently taken to err on the side of caution. Frequently, we will either remove products from shelves or put forth recommendations for modifications of lifestyle in order to provide a maximum margin of safety based upon the best prevalent science available. Yet we have not carried this process forward into the vaccine safety arena.

1. The first effort that should be put forth should be for the Department of Health and Human Services to immediate create and promulgate rules causing a total suspension of exposure to our children of thimerosal, or any other mercury-laden product, until definitive and agreeable scientific evidence supports its utilization in congress with a zero level of suspicion to safety concerns. This to fulfill the US Public Health Services' call to accomplish in 1999, and were supposed to be put forth as recommendations by the Centers for Disease Control in Prevention since 1999 and the Institutes of Medicine in 2000.[150] Yet, nearly five years after their expressing the need to take this position, the CDC has still not formalized nor put forth their relevant recommendation regarding thimerosal and mercury laden devices.

2. In lieu of administrative regulation, legislation could equitably, and possibly preferentially, serve such a purpose, but would be an unfortunate response to a failure by any agency managing such sectors of the public's trust.

3. Either through legislation or administrative regulation, a policy and system of fully informing parents of the benefits and all potential risks associated with any, especially mandatory, vaccinations. Additionally, a full description and discussion of the available remedies for medical, religious and philosophical exemptions should be provided, with a reasonable time for review and reflection, to allow for parents to make a fully informed decision regarding various immunizations for their children.

4. Any state that does not provide for medical, religious and philosophical exemptions in their state immunization and scholastic policies, should immediately undertake legislative efforts to provide such exemptions to their citizens.

5. From congressional hearings, to Institute of Medicine meetings, to peer reviewed efforts, there has been a constant siren call for the adequate and appropriate funding of independent (non-biased) research reviewing these issues. Suggested and appropriate studies must be provided adequate funding to fully investigate all facets of the issue, and the results thereof made public and appropriately incorporated into our public health policies.

6. Having identified the injury, and the path from mercury exposure through thimerosal to autism spectrum disorders, there need to be a focused placed on the size and scope of the effected population. We need to look at those who are suffering and quantify the situation in order to begin accumulating the assets necessary to respond with aid. Families suffering through autism spectrum disorders face a myriad of social, economic

[150] Immunization Safety Review: Thimerosal - Containing Vaccines and Neurodevelopmental Disorders (2001) Institute of Medicine

and relational struggles, many of which are still not fully realized due to the lack of adequate investigation. Forces and resources need to be mobilized in order to bring peace and order into lives where there has been none known.

7. Also regarding research, the Department of Health and Human Services should appropriately, equitably and proportionally, in accordance with the IOM 2001 recommendations for research, fund pharmacokinetic and toxicology studies.

SafeMinds will continue to work towards achieving these recommendations.

Appendices

Appendix A

EPA's List of Mercury Containing Products Used in Medical Laboratories

Mercury Products Used in Medical Laboratories

Test Type	Reagent	Mercury
Albumin		Thimerosal
Drugs of Abuse	All	Thimerosal
Antifungal/Anti-Infectious /Bacteriostatic Enzyme /Ammonia	Merthiolate Mercury Nitrate Mercury Iodide	Thimerosal (26% of Hg).
Herpes EIA	Buffer	Thimerosal
Cytology	Mucolex	Thimerosal
Urine Analysis	Stabilur Tablets	Mercuric Oxide
Hepatitis B Core		Thimerosal
Hepatitis B AG & AB		Thimerosal
Hepatitis C		Thimerosal
HIV		Thimerosal
CA 125		Thimerosal
Progesterone		Thimerosal
Blood Bank Saline	Immu-sal	
Identification of White Cells	Camco	
Clostridium difficile		Thimerosal
Group A *Streptococcus*		Thimerosal
Giardia		Thimerosal
Fixatives	B 5 Fixative Zenker's Solution Helly Ohlamacher Carnoy-Lebrun Shardin	Mercuric Chloride
Histology		Mercuric Chloride
Harris Hematoxylin	Mercuric Oxide	
Antibacterial Agent	Mercurochrome	

EPA's List of Mercury Containing Products Used in Medical Laboratories (continued)

Mercury Products Used in Medical Laboratories

Mercurial Diuretic (known as mercupurin)	Mercurophyline
Flame photomoter (obsolete use)	Mercury Sulfate
Protain Test (contain Hydroxyphenol group)	Millon's Reagent
BUN Test	Nessler's Solution
Enzyme	Nessler's Solution
Non Protein Nitrogen	Nessler's Solution
Pharmaceutical Preservative	Phenol Mercuric Acetate
Takata-ara	Takata's Reagent

Appendix B

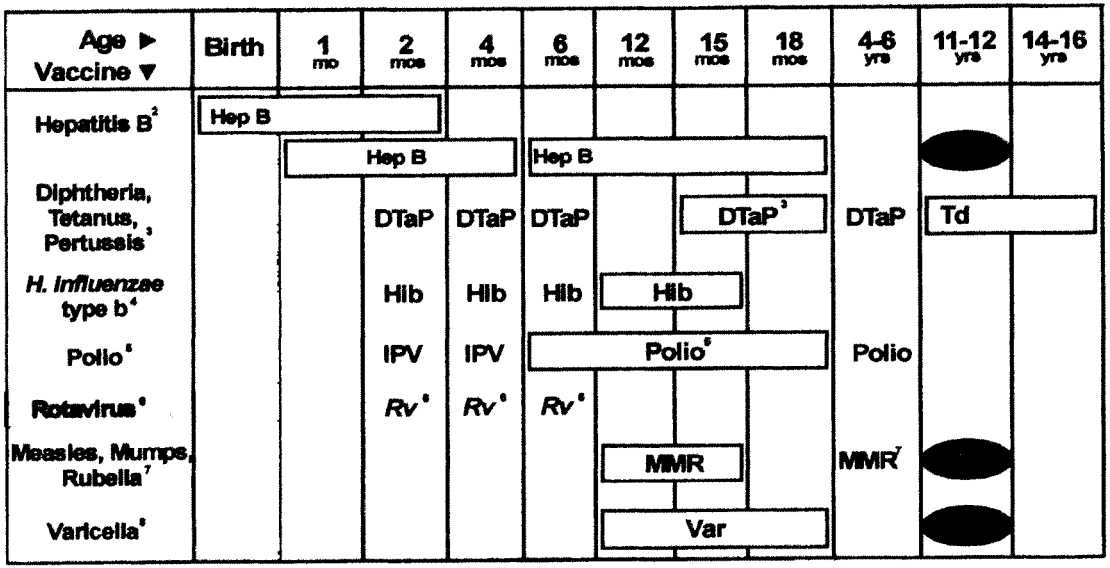
Valid 11/2002 - 01/2003
Sigma Chemical Co.
P.O. Box 14508
St. Louis, MO 63178 USA
Phone: 314-771-5765

M A T E R I A L S A F E T Y D A T A S H E E T

SECTION 1. - - - - - - - - - CHEMICAL IDENTIFICATION- - - - - - - - - -
CATALOG #: T5125
NAME: THIMEROSAL
SECTION 2. - - - - - COMPOSITION/INFORMATION ON INGREDIENTS - - - - - -
CAS #: 54-64-8
MF: C9H9HGNAO2S
EC NO: 200-210-4
SYNONYMS
({O-CARBOXYPHENYL)THIO)ETHYLMERCURY SODIUM SALT * ELICIDE * ETHYL(2-)
TjETBT/PjCourier ACID SODIUM SALT * ETHYLMERCURITHIOSALICYLIC ACID SODIUM
SALT *
ETHYLMERKURITHIOSALICILAN SODNY (CZECH) * ETHYL (SODIUM O-) TjETBT/PjCourier
10 Tf72 MERTHIOLATE SODIUM * MERTORGAN * MERZONIN * MERZONIN SODIUM * SET *
SODIUM ETHYLMERCURIC THIOSALICYLATE * SODIUM O-(ETHYLMERCURITHIO)
BENZOATE * SODIUM ETHYLMERCURITHIOSALICYLATE * SODIUM MERTHIOLATE *
THIMEROSAL * THIMEROSALATE * THIOMERSAL * THIOMERSALATE *
SECTION 3. - - - - - - - - - - HAZARDS IDENTIFICATION - - - - - - - - - -
LABEL PRECAUTIONARY STATEMENTS
HIGHLY TOXIC (USA)
VERY TOXIC (EU)
VERY TOXIC BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.
DANGER OF CUMULATIVE EFFECTS.
MAY CAUSE SENSITIZATION BY INHALATION AND SKIN CONTACT.
IRRITATING TO EYES, RESPIRATORY SYSTEM AND SKIN.
CALIF. PROP. 65 REPRODUCTIVE HAZARD.
TARGET ORGAN(S): NERVES
KIDNEYS
SENSITIZER.
CAUSES IRRITATION.
KEEP AWAY FROM FOOD, DRINK AND ANIMAL FEEDINGSTUFFS.
AFTER CONTACT WITH SKIN, WASH IMMEDIATELY WITH PLENTY OF WATER.
IN CASE OF CONTACT WITH EYES, RINSE IMMEDIATELY WITH PLENTY OF
WATER AND SEEK MEDICAL ADVICE.
WEAR SUITABLE PROTECTIVE CLOTHING.
IN CASE OF ACCIDENT OR IF YOU FEEL UNWELL, SEEK MEDICAL ADVICE
IMMEDIATELY (SHOW THE LABEL WHERE POSSIBLE).
SECTION 4. - - - - - - - - - - FIRST-AID MEASURES- - - - - - - - - - -
IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS CONSCIOUS.
CALL A PHYSICIAN IMMEDIATELY.
IF INHALED, REMOVE TO FRESH AIR. IF NOT BREATHING GIVE ARTIFICIAL
RESPIRATION. IF BREATHING IS DIFFICULT, GIVE OXYGEN.
IN CASE OF SKIN CONTACT, FLUSH WITH COPIOUS AMOUNTS OF WATER
FOR AT LEAST 15 MINUTES. REMOVE CONTAMINATED CLOTHING AND
SHOES. CALL A PHYSICIAN.
IN CASE OF CONTACT WITH EYES, FLUSH WITH COPIOUS AMOUNTS OF WATER
FOR AT LEAST 15 MINUTES. ASSURE ADEQUATE FLUSHING BY SEPARATING
THE EYELIDS WITH FINGERS. CALL A PHYSICIAN.
SECTION 5. --------- FIRE FIGHTING MEASURES ----------

Recommended Childhood Immunization Schedule United States, January - December 1999

Vaccines[1] are listed under routinely recommended ages. Bars indicate range of recommended ages for immunization. Any dose not given at the recommended age should be given as a "catch-up" immunization at any subsequent visit when indicated and feasible. ● indicate vaccines to be given if previously recommended doses were missed or given earlier than the recommended minimum age.



Approved by the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP).

Principal Investigator	Title of Study	Abstract
KININGHAM, KINSLEY K kiningham@marshall.edu MARSHALL UNIVERSITY HUNTINGTON, WV 25701 $137,731 **Funding Cycle:** Fiscal Year 2003 Project Start May 1, 2003 to end April 30, 2006 **Funding ICD:** NIEHS **Grant Number:** 1R15ES012209-01	Mechanism of Thimerosal Induced Neurotoxicity	Mercurials are potent neurotoxins, which localize to both neurons and glia within the central nervous system and elicit a range of deleterious actions. Sodium ethylmercurithiosalicylate (**thimerosal**) is a widely used ethyl mercury containing preservative used in over-the-counter medications, cleaners and cosmetics. Recent concern has been raised on the use of **thimerosal** in over 30 vaccines licensed in the United States. With the addition of several important vaccines over the last few years, exposure to mercury has increased among infants, leading some investigators to suggest an association between **thimerosal** exposure and autism. There is limited toxicological information regarding ethyl mercury; therefore, estimates of health risks from **thimerosal** exposure have been based on mechanistic studies of methyl mercury, a close chemical relative about which much is known. These estimates may actually underestimate the toxicity of ethyl mercury containing agents. The wide use of **thimerosal** makes understanding the mechanism(s) of its toxicity a significant human health issue. The overall goal of this project is to investigate the mechanism by which **thimerosal** causes neuronal cell death. The hypothesis to be tested is that **thimerosal** results in dose-dependent activation of specific signaling molecules and redox-sensitive transcription factors known to activate pro-death genes in neurons. If this hypothesis is correct then pharmacological intervention should attenuate toxicity as a result of **thimerosal** exposure. Using a human neuroblastoma cell line, SK-N-SH, this project will test the hypothesis in four specific aims. Aim 1 will identify in a dose-dependent manner the predominant cell death pathway (apoptotic versus necrotic) associated with **thimerosal** exposure and to determine if it is associated with an increase in reactive oxygen species and caspase-3 dependent. Aim 2 will determine if cell death is mediated through an AP-1-dependent pathway. In addition, this specific aim will establish the role of c-Jun-N-terminal kinase; an enzyme, which phosphorylates and activates AP-1, in **thimerosal**-mediated neuronal death. Aim 3 will determine if the cell death pathway is mediated through an NFkappaB-dependent mechanism. Aim 4 will determine if **thimerosal** toxicity can be attenuated by the administration of S-adenosylmethionine, an enzyme which increases endogenous levels of glutathione. This project will generate mechanistic data on **thimerosal** neurotoxicity and potentially identify specific targets for pharmacological intervention.
MAY, JOAN C. FDA 8 studies Supervisory Chemist FDA/CBER/OVRR/ARC	ANALYSIS AND CHARACTERIZATION OF MERCURY AND TRACE ELEMENTS IN INJECTABLE PRODUCT Analysis and	The goals of this project include: (1) the development of methodology for the quantitative analysis of mercury in various biological products (for example, influenza virus vaccine and immune serum globulin) resulting from the use of mercurial preservatives, (2) develop methodology for the quantitative analysis of the **thimerosal** molecule and any of its degradation products, (3) determine stability of mercury and **thimerosal** in various products, and (4) determine different mercury species present in various products containing **thimerosal** such as Immune Serum Globulin, DTP Vaccine, etc. Cold vapor atomic absorption spectrophotometric methodology has been developed to determine the total mercury resulting from mercurial preservatives such as **thimerosal**, phenylmercuric nitrate and phenylmercuric borate in various injectable biological products. Validation studies for total mercury have been completed for each of the

Principal Investigator	Title of Study	Abstract
Funding Cycle: Annually 1999-2003 **Funding ICD:** CBER/FDA **Grant Number:** 1Z01BR004003-22, 23, 24, 25 1Z01BR004013-01, 1Z01BR004010-01,2, 3	characterization of mercury in injectable products Analysis of mercury in injectable products Development of Organic and Inorganic Analytical Methodol Experiments in Radiation Sterilization	major product types. The cold vapor atomic absorption spectrophotometric procedure used with this sample digestion procedure yields highly accurate and precise results for total mercury in these samples matrices. **Thimerosal** stability studies are being conducted with a number of different biological products. **Thimerosal** has been separated from one of its degradation products, thiosalicyclic acid, by two reverse phase liquid chromatographic procedures. Liquid chromatography with an amperometric detector polarography or gas chromatography/mass spectrometry will be explored as methods for the quantitative and/or structural characterization of the **thimerosal** and its degradation products. Liquid chromatography combined with inductively coupled argon plasma emission spectrometry/mass spectrometry (LC-ICP/MS) has been used to quantitate **thimerosal** in diluent, a Tetanus Toxoid Adsorbed and an Influenza Virus Vaccine. Work is being done on immune serum globulin by this technique. Trace analysis work is being done with phosphorus in conjugate vaccines using inductively coupled argon plasma emission spectrometry. Fluorescence techniques will be applied to the determination of **thimerosal** degradation products in various vaccines. Mercury in various biological products (for example, influenza virus vaccine and immune serum globulin) resulting from the use of mercurial preservatives, (2) develop methodology for the quantitative analysis of the **thimerosal** molecule and any of its degradation products, (3) determine stability of mercury and **thimerosal** in various products, and (4) determine different mercury species present in various products containing **thimerosal** such as Immune Serum Globulin, DTP Vaccine, etc. Cold vapor atomic absorption spectrophotometric methodology has been developed to determine the total mercury resulting from mercurial preservatives such as **thimerosal**, phenylmercuric nitrate and phenylmercuric borate in various injectable biological products. Validation studies for total mercury have been completed for each of the major product types. The cold vapor atomic absorption spectrophotometric procedure used with this sample digestion procedure yields highly accurate and precise results for total mercury in these samples matrices. **Thimerosal** stability studies are being conducted with a number of different biological products. **Thimerosal** has been separated from one of its degradation products, thiosalicyclic acid, by two reverse phase liquid chromatographic procedures. Liquid chromatography with an amperometric detector polarography or gas chromatography/mass spectrometry will be explored as methods for the quantitative and/or structural characterization of the **thimerosal** and its degradation products. Liquid chromatography combined with inductively coupled argon plasma emission spectrometry/mass spectrometry (LC-ICP/MS) has been used to quantitate **thimerosal** in diluent, a Tetanus Toxoid Adsorbed and an Influenza Virus Vaccine. Work is being done on immune serum globulin by this technique. Methods are being developed to detect mercury in vaccines in which mercury has been minimized to meet current safety standards for the use of **thimerosal** in childhood vaccines. Instrumentation is being developed to lower the detection limit of the method. The goal is to determine whether radiation sterilization is able to be used with biological products. It has been approved for use on certain containers and siluents in the past. Studies are being conducted on a

Principal Investigator	Title of Study	Abstract
		cross-section of biological product types using gamma irradiation (cobalt-60), electron beam and X-ray. Emphasis has been placed on childhood vaccines since alternatives to **thimerosal** need to be explored. The research goal is to ensure the safety, purity and potency of vaccines and other biological products through research relating to the development of new or improved accurate, validated, qualitative and/or quantitative methods for the determination and/or characterization of the chemical preservatives, stabilizers, inactivators, adjuvants, residual moisture, protein and other chemical constituents of vaccines and biological products regulated by CBER and subject to license or release action. Improved methodologies include chromatographic, thermogravimetric, spectroscopic and mass spectomeric methods of analysis. Determination of residual moisture in freeze-dried biological products. The goal of this project is to develop new or improved methods for the determination of moisture in biological products. A low residual moisture is necessary for the stability, viability and potency of the freeze-dried biological product. The residual moisture of freeze-dried biological products was first determined by the gravimetric or loss-on-drying method utilizing phosphorus pentoxide and vacuum at room temperature. This method has been optimized. For samples with uncomplicated thermogravimetric analysis (TG) curves, TG results have been shown to correlate with coulometric Karl Fischer results. Karl Fischer and TG moisture results may be different from the gravimetric moisture result for the same freeze-dried product due to the fact that different types of moisture (physically adsorbed or chemically bound moisture) are being measured. The thermogravimetric method has been used to determine the moisture content of Group A and Group C Meningococcal Polysaccharide bulks at levels of 5% to 25% moisture. Thermogravimetric/mass spectrometry (TG/MS) identified the TG transition corresponding to the loss of residual moisture in vaccines that have complex TG curves. Thermogravimetry provides precise heating conditions and weight loss information at specified temperatures while mass spectrometry identifies volatile compounds evolved during the weight loss process. A new TG/MS interface applicable to this analysis has been developed in our laboratory. The glass tubing interface connects the quartz combustion tube of the TG to the jet separator of the mass spectrometer. This interface allows continuous monitoring of the ion intensities of mass peaks m/e=18 (water) and m/e=44 (carbon dioxide) for the determination of residual moisture in freeze-dried biological products. Data has been collected clarifying thermograms for both Giant Short Ragweed Allergenic Extracts as well as Limulus Amebocyte Lysate Haemophilus b. Polysaccharide Conjugate Vaccines and other products such as Allergen Patch Test. A new TG/MS capillary interface has been developed and applied to moisture analysis for AHF and BCG vaccine. A method is being researched that will determine moisture in space above freeze-dried cake in the vial. This vapor pressure moisture methodology is being applied to the study of the redistribution of moisture between cake, head-space and stopper or head-space and cake over time. A new aspect of this project involves correlating residual moisture values calculated thermodynamically with values obtained experimentally. Near infrared Spectrometry (NIR) is being evaluated for its application to moisture determination in the freeze-dried vaccine final container. Analysis and characterization of mercury in injectable products. The goals of this project include: (1) the development of methodology for the quantitative analysis of mercury in various

Principal Investigator	Title of Study	Abstract
		biological products (for example, influenza virus vaccine and immune serum globulin) resulting from the use of mercurial preservatives, (2) develop methodology for the quantitative analysis of the **thimerosal** molecule and any of its degradation products, (3) determine stability of mercury and **thimerosal** in various products, and (4) determine different mercury species present in various products containing **thimerosal** such as Immune Serum Globulin, DTP Vaccine, etc. Cold vapor atomic absorption spectrophotometric methodology has been developed to determine the total mercury resulting from mercurial preservatives such as **thimerosal**, phenylmercuric nitrate and phenylmercuric borate in various injectable biological products. Validation studies for total mercury have been completed for each of the major product types. The cold vapor atomic absorption spectrophotometric procedure used with this sample digestion procedure yields highly accurate and precise results for total mercury in these samples matrices. **Thimerosal** stability studies are being conducted with a number of different biological products. **Thimerosal** has been separated from one of its degradation products, thiosalicyclic acid, by two reverse phase liquid chromatographic procedures. Liquid chromatography with an amperometric detector polarography or gas chromatography/mass spectrometry will be explored as methods for the quantitative and/or structural characterization of the **thimerosal** and its degradation products. Liquid chromatography combined with inductively coupled argon plasma emission spectrometry/mass spectrometry (LC-ICP/MS) has been used to quantitate **thimerosal** in diluent, a Tetanus Toxoid Adsorbed and an Influenza Virus Vaccine. Work is being done on immune serum globulin by this technique. Methods are being developed to detect mercury in vaccines in which mercury has been minimized to meet current safety standards for the use of **thimerosal** in childhood vaccines. Instrumentation is being developed to lower the detection limit of the method. Determination of trace metals in injectable biological products. The objectives of this project are to develop and validate methodologies for the determination of trace metals in injectable biological products. This includes trace metals present as residuals of the manufacturing procedure, those present as impurities and those that are chemical constituents of biological products whose concentration is vital to product stability, efficacy or safety. Methodology used includes atomic absorption spectrometry, inductively coupled argon plasma emission spectrometry, inductively coupled argon plasma mass spectometry and ion chromatography. An interagency agreement with NIST resulted in data which gives the trace metal profile for a number of biological products. This survey identified high levels of aluminum in several albumins from one manufacturer. Toxicologists at FDA evaluated the data collected. A new objective involves evaluating the trace metal leachates from several types of glass vials including vials lined with silican dioxide coatings and glass vials fabricated with cerium. An ICP method has been developed for phosphorus in Haemphilus b Conjugate Vaccine. Work has been done on the determination of low levels of copper in Mega 1 and Mega 2 international standards for Antihemophilic Factor. Experiments in Radiation Sterilization. The goal is to determine whether radiation sterilization is able to be used with biological products. It has been approved for use on certain containers and diluents in the past. Studies are being conducted on a cross-section of biological product types using gamma irradiation (cobalt-60), electron beam and x-ray. Emphasis has been placed on childhood vaccines since alternatives to **thimerosal** need to be explored. Analysis and characterization of organic chemical constituents of

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		injectable products. The project is led by Anthony Ciavarella. This research focuses on the quantitative analysis and characterization of the chemical components in vaccines including 2-phenoxyethanol. 2-Phenoxyethanol is used as a preservative in vaccines which include Hepatitis, Polio, and DTaP(Diphtheria and Tetanus Toxoids and Acellular Pertussis). To ensure the proper amount of this preservative, we have modified the USP<341> Antimicrobial Agents method to use in the quantitation of 2-phenoxyethanol. Current work includes the validation of this packed column GC method under ICH guidelines which is nearing completion. Future research will involve the development of a capillary GC method resulting in greater accuracy and column efficiency. Analytical methods for the determination of transmissible spongiform encelphalopathy (TSE) agent infectivity in differentiated neuronal cell cultures. Led by Alfred Del Grosso. This work had involved the determination of acetylcholinesterase and tyrosine hydroxylase activities and related methods development in collaborative support of project number Z01 BR05008-02 LMD, "Potential assay of transmissible spongiform encephalopathy (TSE) agent infectivity in differentiated neuronal cell cultures". Acetylcholinesterase determinations were performed by the method of G. Ellman (Biochem. Pharm. 7, 88-95, 1961). Tyrosine hydroxylase activity is measured by determination of the enzyme product DOPA (dihydroxyphenylalanine) by HPLC. In this procedure, incubation was performed in the presence of saturating concentrations of tyrosine substrate and 6-methyltetrahydropteridine cofactor; DOPA product was determined by reverse phase HPLC with amperometric electrochemical detection after bulk extraction with acidic alumina. In FY00 and 01, the method was modified based on the studies of D. Hooper in which signal-to-noise levels were improved with the addition of glycerol to reduce blank values and dihydropteridine reductase and NADPH for regeneration of the tetrahydropteridine cofactor. Determination of total protein, for the purpose of normalizing enzyme activities to the concentration of cell culture, is being performed by a micro BCA (bichoninic acid) procedure. Determinations of acetylcholinesterase activity in scrapie inoculated PC12 cell culture have not to date shown a significant difference in activity from those obtained from un-inoculated cultures. These results are to be described along with modifications to the chromatographic determination of tyrosine hydroxylase activity. Further activity has been suspended with the retirement of Jeanette Ridge, PI for project Z01 BR05008-02. Chromatographic determination of chemical components of biological products. Led by Alfred Del Grosso. The objectives of this project are to develop and validate methodologies for chemical components of biological products whose concentration is vital to product stability, efficacy or safety. These include: 1) phenol used as an antimicrobial preservative in multi-use parenterals such as allergenic extracts and bacterial vaccines, 2) glycerin used in allergenic extracts as a preservative and/or stabilizer, 3) 2-phenoxyethanol used as a preservative in inactivated poliovirus vaccine and combined bacterial vaccines, 4) formaldehyde used as an inactivating agent in influenza virus vaccine, hepatitis B vaccine and other products, 5) chloride in human serum albumin and dextran volume expanders, 6) histamine in positive skin test control, 7) organic, natural product and complex synthetic mixture components of allergen patch tests. Current work in progress includes the following methods development and validation activities: 1) The complete validation of CBER gas chromatographic methods based on USP <1225> "Antimicrobial Agents - Content" for 2-phenoxyethanol. Under A. Del Grosso's

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		direction, A. Ciavarella has validated this procedure for accuracy, precision and specificity. An evaluation of robustness and ruggedness parameters is on-going. Future plans will include the evaluation of wide-bore capillary columns to provide faster analysis and enhanced specificity through higher chromatographic efficiency. 2) An HPLC procedure for glycerin has provided lower analytical results relative to potentiometric titration when applied to food allergenic extracts. Analytical recoveries by the different techniques are being compared along with procedural modifications to enhance recovery. 3) The development of a procedure for monosaccharide composition analysis of neutral sugars in purified proteins. Preliminary results using a procedure involving selected ion monitoring capillary gas chromatography of per-trimethylsilylated saccharides indicate that composition analysis from 10 micrograms of protein, representing ca. 200 nanograms total carbohydrate should be feasible. 4) The evaluation of gas chromatography with pulsed discharge detection as a potential procedure for low levels of formaldehyde in vaccine products. Identification and quantitation of impurities and residual manufacturing agents in biological products. Led by Alfred Del Grosso. The objectives of this project are to develop and validate methodologies for chemical impurities and residual manufacturing agents in biological products whose presence may affect product safety or efficacy. These include: 1) residual glutaraldehyde used as inactivating or conjugating agent in vaccines, 2) residual tetrachloroethylene in pollen allergenic extracts and allergenic source materials, 3) inactive components of crude allergenic extracts and allergen patch test materials and 4) lipopolysaccharides (endotoxins) in allergenic extracts and vaccines. Current work in progress, or that performed in the past year includes: 1) The determination of perchloroethylene content in allergenic extracts and pollen source materials. Perchloroethylene is used in the processing of pollen source materials for allergenic extracts. A dynamic headspace gas chromatographic method for tetrachloroethylene in allergenic extracts has been developed and validated, data has been obtained for a representative sampling of final products. The determination of this same compound in allergenic source materials by gas chromatography/mass spectrometry has been validated and data on a representative sampling of pollen source materials has been collected. 2) An HPLC method for the determination of glutaraldehyde, involving pre-column derivatization with p-nitrobenzyl-hydroxylamine and UV detection has been developed and validated as a limits test at 100ppb. 3) A recently acquired ion-trap HPLC/mass spectrometer will be used along with gas chromatography/mass spectrometry to develop a general procedure for impurities screening in a variety of products as well as the characterization of low-molecular weight compounds in allergenic extracts and allergen patch test products. 4) Several chromatographic and mass spectrometric techniques are being evaluated for the determination of lipopolysaccharide content of allergenic extracts and vaccines based on characteristic 3-hydroxy fatty acid marker compounds. Determination of nitrogen content (protein content) of vaccines and other biological products. Led by Nora Etz. This study was initiated with the following objectives: (1) to standardize the protein nitrogen unit PNU method for the determination of the concentration of allergenic extracts, (2) to determine the stability of the allergenic extract PNU value throughout the dating period, (3) to determine between laboratory reproducibility for assayed PNU values, and (4) to improve the detection limit for the determination of nitrogen and decrease analysis time. Parameters were optimized for the PNU

Principal Investigator	Title of Study	Abstract
		precipitation procedure for aqueous, freeze-dried, glycerinated and alum precipitated allergenic extracts. The stability study indicated stability for PNU values when the products tested have been stored at a constant 2-8oC. Although the allergens lose their reactivity with time, the PNU value does not change significantly. It is an estimate of the concentration of a freshly prepared allergenic extract. The collaborative study of the optimized PNU precipitation procedure consisted of the analysis of six samples in duplicate by six laboratories using the CBER Kjeldahl methodology. Methodology is being studied to determine the protein content in Anthrax Vaccine, Typhoid Vaccine, Cholera Vaccine, Influenza Virus Vaccine and other vaccines such as Hepatitis B Vaccine and Hepatitis C100-3 Antigen in which protein measurement by the Lowry method would be subjected to interferences by compounds which are present such as SDS, Tris, EDTA, and thiol reagents (DTT and **thimerosal**). A study of the above methods is underway. This project incorporates FY2002 projects 1Z01BR004002-27, 1Z01BR004003-25, 1Z01BR004004-24, 1Z01BR004005-17, 1Z01BR004006-17, 1Z01BR004007-15, 1Z01BR004008-15, and 1Z01BR004010-03.
PESSAH, ISAAC 3 Studies ipessah@ucdavis.edu UNIVERSITY OF CALIFORNIA DAVIS **Funding Cycle:** 2001 (30 Sept 2001 through 29 Sept 2006) 2002 2002 **Funding ICD:** NIEHS **Grant Number:** 1P01ES011269-010003 3P01ES011269-01S10003 5P01ES011269-020003	Molecular and cellular mechanisms of autism (Identical title and abstracts for each grant)	The long-term goal of Research Project III is to identify molecular and cellular mechanisms that underlie idiosyncratic responses within autistic children to chemicals to which they are exposed in in utero and during periods of early postnatal brain development. The pressing worldwide concern about the role of vaccine antigens, the mercurial preservative **thimerosal**, and environmental exposure to mixtures of methylmercury and PCBs, justify detailed analysis of the underlying mechanisms of these factors in autism. We will first focus on three hypotheses relating to synergistic actions of mercurials and PCBs agents, known to be immunotoxic and neurotoxic. The hypotheses to be tested are: Hypothesis I addresses how peripheral blood mononuclear cells (PBMCs) from autistic children exhibit significant differences in their sensitivity and/or pattern of cell activation and cytokine secretion when challenged in vitro with vaccine antigens. How Non-coplanar PCBs of environmental relevance, **thimerosal** and other environmental agents identified by the Center's units exacerbate these differences will be studied. Hypothesis II determines how organic mercurials (**thimerosal** and MeHg) and non-coplanar PCBs (PCBs 118, 138, 153, 170, and 180 singly or in combination) act synergistically to influence glia/neural cell signaling pathways leading to altered patterns of dendritic spine growth, dendritic branching and synaptogenesis. Products of antigen- stimulated and control PBMCs (isolated from autistic and non-autistic children) characterized and quantified in Hypothesis I will be used to address their differential effects on neuronal cell growth. Hypothesis III utilizes mice exposed to PCBs and organic mercurials in vivo (PROJECT II) to assess functional and biochemical changes associated with social behavioral deficits. We will identify differences in patterns of evoked potentials and excitability in hippocampus/amygdala slice preparations from mice that have been perinatally or neonatally exposed to PCBs, organic mercurials, singly or in combination in Project II. We will elucidate the underlying biochemical mechanisms of these effects.
AMARAL, DAVID 3 Studies dgamaral@ucdavis.ed	Animal Models of Autism	Autism is a neurodevelopmental syndrome defined by deficits in social reciprocity and communication and by unusual repetitive behaviors. While there is clearly an underlying genetic predisposition, the etiology(ies) of autism is/are currently unknown. Development of animal models of autism have been

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u University of California at Davis **Funding Cycle:** 2001 2002 2002 To begin 30 Sept 2001 and end 29 Sept 2006 **Funding ICD:** NIEHS **Grant Number:** 1P01ES011269-010002 3P01ES011269-01S10002 5P01ES011269-020002		hobbled by the lack of knowledge concerning its etiology(ies) and by the paucity of data on the characteristic neuropathology of autism, i.e., it is not clear what a successful model of autism would look like. If one focuses on the root deficit in autism, i.e., the impairment of social interaction, however, successful mouse and nonhuman primate models are achievable. The overarching goal of this project is to establish batteries of behavioral tasks that will provide sensitive assessments of normal mouse and rhesus monkey social behavior. With the establishment of the animal models, two hypotheses will be tested: 1) that prenatal and/or postnatal exposure to xenobiotics will decrease normal conspecific social behavior; and 2) that changes in social behavior will be associated with alterations of brain regions, such as the amygdala, that have been implicated in social behavior. Perinatal mice will be parametrically exposed to **thimerosal**, methyl mercury, and to a mixture of PCB congeners (PCB 153, 180, 118, 138, and 170) to determine whether these xenobiotics alter normal social behavior. Based, in part, on the mouse studies and on information concerning expected environmental exposure in autistic children, neonatal monkeys will also be exposed to **thimerosal**, methyl mercury and PCBs. The mouse battery of social and cognitive testing will include: Response to maternal separation and relocation; response to maternal separation and relocation; response to novel objects; response to a human intruder; response to social videotapes. A specially designed ethogram will also be used to evaluate maternal <->infant interactions and to study the emergence and quality of social behaviors through daily dyadic social interactions with "stimulus" animals. At the termination of behavioral testing, morphological changes will be evaluated in brain regions, such as the amygdala, known to be involved in normal social behavior. Additional tissue will be distributed to Core I for analysis of xenobiotic distribution, to Core II for analysis of cytokines and autoantibody production and Core III for altered brain gene expression.
LUECKE, ARTMUT 3 Studies Stanford University (These do not appear directly related to thimerosal toxicity) **Funding Cycle:** 2001 2002 2002 **Funding ICD:** NCRR **Grant Number:** 5P41RR001209-220021 5P41RR001209-230021	STAFF PRIORITY TIME XRAY STRUCT ANALYSIS OF INOSINEMONOPHOSPHATE DEHYDROGENASE	Inosine monophosphate dehydrogenase (IMPDH) catalyzes the NAD-dependent oxidation of inosine monophosphate (IMP) to xanthine monophosphate (XMP). This is the rate-limiting step in purine biosynthesis. Inhibitors of this enzyme have been shown to have anti-tumor, immunosuppressive, and antiparasitic effects. Inhibition of T. foetus IMPDH in vitro arrests the growth of the organism and this inhibition can be overcome by supplementing the medium with GMP. Native, derivative, and complex data were collected at 7-1 at SSRL. Good **thimerosal**, PCMBS and tetra-chloro-platinate derivative data sets were obtained and used for MIR phasing. Initial low-resolution SIR and MIR electron density maps indicated a flat, tetrameric molecule, consistent with the expected crystal packing where there is one 503 amino-acid monomer in the asymmetric unit, and the tetramer is generated by the crystallographic four-fold operator. Each monomer forms an a/b barrel resembling very closely the a/b barrel of triose phosphate isomerase (TIM barrel). Subsequent phase combination with the MIR and refined partial model phases has allowed us to fit most of the amino acid backbone and side chains. Heavy-atom difference maps indicate clearly 5 cysteine residues that reacted with either PCMBS or **thimerosal**, and 3 methionine residues that bound platinum chloride. The active site has been identified by the position of an active-site cysteine and the positions of electron density in difference maps calculated from data collected on ligand and inhibitor-soaked crystals.

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3P41RR001209-23S10021		
HARRY, GAYLIA 2 Studies ACTING CHIEF LABORATORY OF MOLECULAR TOX **Funding Cycle:** 2002 2003 **Funding ICD:** NIEHS **Grant Number:** 1Z01ES021164-06 1Z01ES021164-07	Environmentally Induced Alterations In Neuron And Glia D	The susceptibility of the developing nervous system to environmental agents has been a major concern with regard to children's health issues. While current exposure levels to environmental agents does not represent an acute injury, disruption to the nervous system may be associated with either a structural alteration in the formation of the neural network and/or in nervous system functioning. It is the goal of this project to develop and validate test methods that will allow us to assess various types of chemical-induced perturbations of the brain during development. The formation and interactions between the various cell types in the brain are critically timed events.Such windows of vulnerability is assummed to be a major component in the differential susceptibility of the developing organism to environmental insult. This project examines chemical induced perturbations during development of the nevous as indicated by alterations in the spatio-temporal expression of mRNA for various developmentally regulated proteins associated with distinct processes of development, distribution of compounds to the nervous system, and the neurobehavioral outcome of such exposure. The specific projects under study include 1) distribution of mercury to the brain of young animals following the intramuscular injection of various mercuricals. 2) alterations in the neurobehavioral functioning following early exposure to the pro-inflammatory cytokine IL-6 as a model of maternal infection and premature delivery. 3) Alterations in neuronal processes in the brain following exposure to compounds that perturb homeostatic maintenance of thyroid hormone during gestational and postnatal development. With regard to delivery of mercury to the brain following an intramuscular injection of either methyl mercury, ethyl mercury, **thimerosal**, as compared to an oral administration of methyl mercury demonstrated a distribution pattern distinct between the two routes of exposure suggesting a sequestration of the metal within the muscle resulting a minimal level within the brain. Neuroinflammation in the young mouse brain as generated by a direct delivery of hyper-IL6 to the cortical layer resulted in subtle alterations in neurobehavioral functioning characterized by a hyper-reactivity to environmental stimuli and a relatively inflexibility in learning and performance that continued in the adult animal. Alterations in thyroid hormone levels during gestation and lactation induced by either hexachlorobenzene or PCBs produced distinct patterns of disruption in cerebellar neurons as demonstrated by Golgi staining of neuronal processes. For PCBs this pattern of disruption was transient and may be linked to the period of active development. Early developmental exposure to inorganic lead is known to alter brain development. Based upon our previous studies examining specific neuronal and glia markers following low level lead exposure we initiated a study to examine in a more broad manner the developmental ontogeny of multiple nervous system specific genes using DNA array techniques. One specific finding of these studies was the shift in the developmental pattern for a specific chlorid plexus gene suggesting an early maturation of the chlorid plexus as a protective mechanism against a heavy metal exposure however, the consequences to such an early maturation is yet to be studied. For these studies we have used a number of methods to examine alterations in the developing nervous system following exposure to environmental agents including immunohistochemistry, molecular techniques to examine mRNA levels, as well as assessment of neurobehavioral functioning.

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ETZ, NORA 4 Studies **Funding Cycle:** 1999 2000 2001 2002 **Funding ICD:** CBER/FDA **Grant Number:** 1Z01BR004008-12, 13, 14, 15	DETERMINATION OF NITROGEN CONTENT (PROTEIN CONTENT) OF BIOLOGICAL PRODUCTS	This study was initiated with the following objectives: (1) to standardize the protein nitrogen unit PNU method for the determination of the concentration of allergenic extracts, (2) to determine the stability of the allergenic extract PNU value throughout the dating period, (3) to determine between laboratory reproducibility for assayed PNU values, and (4) to improve the detection limit for the determination of nitrogen and decrease analysis time. Parameters were optimized for the PNU precipitation procedure for aqueous, freeze-dried, glycerinated and alum precipitated allergenic extracts. The stability study indicated stability for PNU values when the products tested have been stored at a constant 2-8oC. Although the allergens lose their reactivity with time, the PNU value does not change significantly. It is an estimate of the concentration of a freshly prepared allergenic extract. The collaborative study of the optimized PNU precipitation procedure consisted of the analysis of six samples in duplicate by six laboratories using the CBER Kjeldahl methodology. A chemiluminescence method is being explored as a method for nitrogen determination that is more sensitive than the micro-Kjeldahl method and which can detect about 10 micrograms of protein/mL or 1.6 micrograms of nitrogen/mL. Methodology is being studied to determine the protein content in protein in Typhoid Vaccine, Cholera Vaccine, and other vaccines such as Hepatitis B Vaccine and Hepatitis C100-3 Antigen in which protein measurement by the Lowry method would be subjected to interferences by compounds which are present such as SDS, Tris, EDTA, and thiol reagents (DTT and **thimerosal**). A study of the above methods is underway. ay.
HAN, SEUNGIL Stanford University (This does not appear to be related to the thimerosal-toxicity dialogue) **Funding Cycle:** 1999 **Funding ICD:** NCRR **Grant Number:** 5P41RR001209-200162	STRUCT DETERMINATION OF NOVEL ADP RIBOSYLATING TOXIN FROM BACILLUS THURINGIENSIS	ADP-ribosylating toxins have been studied as a key to prevention and treatment of diseases caused by the toxin-producing infectious microorganisms, and these toxins have provided unique pathological tools for the study of the physiological functions fo their target proteins. Recently, we have purified and crystallized a novel ADP-ribosylating toxin from Bacillus thuringiensis which is not homologous to other known ADP-ribosylating toxin. The crystals can be successfully flash-frozen using 30% PEG200 as a cryo-precipitant and 3.5 E resolution data set has been collected using our local laboratory X-ray source. We also obtained three heavy atom derivatives, **thimerosal**, trimethyl lead acetate, and K2IrCl6 which crystals diffract only to about 4 E resolution.

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May Joan C 17 Studies **Funding Cycle:** 1990 1991 1992 1993 1994 1995 1996 1998 1991 1992 1993 1994 1995 1996 1997 1998 **Funding ICD:** CBER/FDA **Grant Number:** 1Z01BB001001-13, 14, 15, 16, 17, 18, 19, 20 1Z01BB001010-01, 2, 6, 7, 8, 9 10, 11	ANALYSIS AND CHARACTERIZATION OF MERCURIAL PRESERVATIVES IN INJECTABLES DETERMINATION OF NITROGEN CONTENT (PROTEIN) OF BIOLOGICAL PRODUCTS	*The goals of this project include: (1) the development of methodology for the quantitative analysis of mercury in various biological products (for example, influenza virus vaccine and immune serum globulin) resulting from the use of mercurial preservatives, (2) develop methodology for the quantitative analysis of the* ***thimerosal*** *molecule and any of its degradation products, (3) determine stability of mercury and* ***thimerosal*** *in various products, and (4) determine the different mercury species present in various products containing* ***thimerosal*** *such as Immune Serum Globulin, DTP Vaccine, etc. Cold vapor atomic absorption spectrophotometric methodology has been developed to determine the total mercury resulting from mercurial preservatives such as* ***thimerosal****, phenylmercuric nitrate and phenylmercuric borate in various injectable biological products. Validation studies for total mercury have been completed for each of the major product types. The cold vapor atomic absorption spectrophotometric procedure used with this sample digestion procedure yields highly accurate and precise results for total mercury in these sample matrices.* ***Thimerosal*** *stability studies are being conducted with a number of different biological products.* ***Thimerosal*** *has been separated from one of its degradation products, thiosalicyclic acid, by two reverse phase liquid chromatographic procedures. Liquid chromatography with an amperometric detector, polarography or gas chromatography/mass spectrometry will be explored as methods for the quantitative and/or structural characterization of the* ***thimerosal*** *and its degradation products. Liquid chromatography combined with inductively coupled argon plasma emission spectrometry/mass spectrometry (LC-ICP/MS) has been used to quantitate* ***thimerosal*** *in diluent, a Tetanus Toxoid Adsorbed and an Influenza Virus Vaccine. Work is being done on immune serum globulins by this technique.* *This study was initiated with the following objectives: (1) to standardize the protein nitrogen unit PNU method for the determination of the concentration of allergenic extracts, (2) to determine the stability of the allergenic extract PNU value throughout the dating period, (3) to determine between laboratory reproducibility for assayed PNI values, and (4) to improve the detection limit for the determination of nitrogen and decrease analysis time. Parameters were optimized for the PNU precipitation procedure for aqueous, freeze-dried, glycerinated and alum precipitated allergenic extracts. The stability study indicated stability for PNU values when the products tested have been stored at a constant 2-8 degrees C. Although the allergens lose their reactivity with time, the PNU value does not change significantly. It is an estimate of the concentration of a freshly prepared allergenic extract. The collaborative study of the optimized PNU precipitation procedure consisted of the analysis of six samples in duplicate by six laboratories using the CBER Kjeldahl methodology. A chemiluminescence method is being explored as a method for nitrogen determination that is more sensitive than the micro-Kjeldahl method and which can detect about 10 micrograms of protein/mL or 1.6 micrograms of nitrogen/mL. Methodology is being studied to determine the protein content in protein in Typhoid Vaccine, Cholera Vaccine, and other vaccines such as Hepatitis B Vaccine and Hepatitis C100-3 Antigen in which protein measurement by the Lowry method would be subjected to interferences by compounds which are present such as SDS, Tris, EDTA, and thiol reagents*

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		*(DTT and **thimerosal**). A study of the above methods as well as an OPA assay is underway.*
KEARNS, D 2 Studied **Funding Cycle:** 1991 1992 **Funding ICD:** CBER/FDA **Grant Number:** 1Z01BE001005-01, 2	FUNGISTASIS TESTING OF SOME BIOLOGICAL PRODUCTS	*Eleven products were tested. For the Diphtheria Antitoxin, Epoetin Alfa Epogen, Tetanus Antitoxin, Interferon Alfa 2b Recombinant, G-CSF, and Streptokinase, the A. niger grew out in SCDM and FTM, thus showing that at this dilution (1 in 11), there was no fungistatic effect. For Influenza Virus Vaccine, Hepatitis B Vaccine Recombinant, Pneumococcal Vaccine Polyvalent, and Tetanus and Diphtheria Toxoids Adsorbed, the A. niger grew only in the bottles of FTM. This is an expected result since these products contain **thimerosal**, which thioglycollate neutralizes. The exception to this is the Hepatitis B Vaccine which only has formaldehyde listed in its protocol, not **thimerosal**, and did not grow out in SCDM. The Diphtheria and Tetanus Toxoids and Pertussis Vaccine is the only product that would not allow the A. niger to grow in either media, not even at a product dilution of 1 in 50. Therefore, the sterility test for DTP, which used a dilution factor of approximately 1 in 80, will have to be checked at that dilution. We will continue this testing as time allows to be sure that products with preservative are being adequately diluted in the sterility test.*
LUECKE, HARTMUT **Funding Cycle:** 1996 **Funding ICD:** NCRR **Grant Number:** 5P41RR001209-170014	STAFF TIME: INOSINE MONOPHOSPHAT E DEHYDROGENAS E FR PARASITE TRICHOMONAS FEOTUS	*Inosine monophosphate dehydrogenase (IMPDH) catalyzes the NAD-dependent oxidation of inosine monophosphate (IMP) to xanthine monophosphate (XMP). This is the rate-limiting step in purine biosynthesis. Inhibitors of this enzyme have been shown to have anti-tumor, immunosuppressive, and antiparasitic effects. Inhibition of T. foetus IMPDH in vitro arrests the growth of the organism and this inhibition can be overcome by supplementing the medium with GMP. Native and derivative data were collected at 7-1 at SSRL. Good **thimerosal**, PCMBS and tetra-chloro-platinate derivative data sets were obtained and used for MIR phasing. Initial low-resolution SIR and MIR electron density maps indicated a flat, tetrameric molecule, consistent with the expected crystal packing where there is one 503 amino-acid monomer in the asymmetric unit, and the tetramer is generated by the crystallographic four-fold operator. Each monomer forms an a/b barrel resembling very closely the a/b barrel of triose phosphate isomerase (TIM barrel). Subsequent phase combination with the MIR and refined partial model phases has allowed us to fit most of the amino acid backbone and side chains. Heavy-atom difference maps indicate clearly 5 cysteine residues that reacted with either PCMBS or **thimerosal**, and 3 methionine residues that bound platinum chloride. In addition, the active site has been identified by the position of an active-site cysteine and the positions of electron density in difference maps calculated from data collected on ligand and inhibitor-soaked crystals.*
ASKARI, AMIR 15 Studies Chairman MEDICAL COLLEGE OF OHIO AT TOLEDO mbeck *a* mco edu **Funding Cycle:** 1980	EFFECTS OF MERCURIAL POISONS ON NA+, K+-ATPASE CARDIAC GLYCOSIDES: MECHANISMS OF	*Na plus, K ions-ATPase, an enzyme of the plasma membrane, is involved in the regulation of the internal ionic environment of most mammalian cells. Our previous work on the interactions of short-chain alkylmercury compounds, such as methylmercury and **ethylmercury**, with this enzyme has shown that (a) these mercurials inhibit the Na plus K ions-dependent ATPase activity of the enzyme without inhibiting its partial reactions; and (b) these unique effects of the mercurials are due to the disruption of the quaternary structure of the enzyme. The specific aim of this proposal is to utilize the mercurials as tools for the study of the quaternary structure of the enzyme, and the relation of this to the enzyme's function. Experiments will be done (a) on the kinetics of the reactions catalyzed by the mercurial-modified enzyme, and on the kinetics of ligand binding to the enzyme, in order to determine the nature of the intersubunit and intersite*

Principal Investigator	Title of Study	Abstract
1981 1982 1983 1984 Started 1 Aug 1977 Ended 31 July 1985 1978 1979 1980 1981 1982 1983 1984 1985 Started 1 Sept 1978 Ended 31 Aug 1981 1985 **Funding ICD:** NIEHS NHLBI NHLBI NHBLI **Grant Number:** 2R01ES001599-04 5R01ES001599-05, 6, 7, 8, 2R01HL019129-04, 5, 6, 7, 8, 9, 10, 11, 2 9R01HL034284-09 5R01HL019129-02	CELLULAR ACTIONS REGULATION OF NAK-ATPASE	*interactions; (b) to attempt the solubilization of the mercurial-modified enzyme in order to purify and characterize the enzyme's protomers; (c) to determine the number of catalytic subunits of the native enzyme, and whether all subunits are identical or not, through cross-linking experiments on the native and the mercurial-modified enzyme; and (d) to establish the relation of enzyme's subunit composition to its transport function by measuring Na plus, K ions-fluxes in resealed red cell membranes in which some of the enzyme subunits have been cross-linked. The long-range goals of this project are: 1. Understanding of the mechanism of the active transports of Na plus and K ions across the cell membrane. 2. Elucidation of the mechanisms of molecular and cellular effects of a group of environmental hazards; namely, the short-chain alkylmercury compounds.* *The general aim of this project is the elucidation of the mechanism of action of cardiac glycosides at the cellular and the molecular levels. Attention is focused on the interaction of these drugs with Na ion, K ion-ATPase of the cell membrane. The specific projects proposed are: 1. Using the fluorimetric assay of methylfluorescine phosphatase for the determination of extent of inhibition of enzyme in drug-exposed dog and rabbit hearts, the relation of positive inotropic effects of cardiac glycosides to their inhibitory effects on Na ion, K ion-ATPase will be re-examined. 2. Through studies on the kinetics of cardiac glycoside interaction with the enzyme of intact human red cells, the determination of the mechanism of effect of extracellular K ion on this drug-receptor interaction; and the elucidation of the cause of extreme stability of this drug receptor complex in the intact cell, will be attempted. 3. Effects of cardiac glycosides on enzymes prepared from Purkinje fibers of the hearts of newborn and adult dogs will be studied, to determine if different drug-sensitivities of these enzymes can account for the different responses of these hearts to cardiac glycosides. 4. To learn more about the molecular bases of different sensitivities of various purified enzymes to cardiac glycosides, the properties of three enzymes with known differences in drug sensitivities will be compared. These are the native dog kidney enzyme, the native rat kidney enzyme, and the dog kidney enzyme whose ATP-regulatory site has been blocked through reaction with* ***ethylmercury****.* *Na plus, K ions-ATPase, an enzyme of the plasma membrane, is involved in the regulation of the internal ionic environment of most mammalian cells. Our previous work on the interactions of short-chain alkylmercury compounds, such as methylmercury and* ***ethylmercury****, with this enzyme has shown that (a) these mercurials inhibit the Na plus K ions-dependent ATPase activity of the enzyme without inhibiting its partial reactions; and (b) these unique effects of the mercurials are due to the disruption of the quaternary structure of the enzyme. The specific aim of this proposal is to utilize the mercurials as tools for the study of the quaternary structure of the enzyme, and the relation of this to the enzyme's function. Experiments will be done (a) on the kinetics of the reactions catalyzed by the mercurial-modified enzyme, and on the kinetics of ligand binding to the enzyme, in order to determine the nature of the intersubunit and intersite interactions; (b) to attempt the solubilization of the mercurial-modified enzyme in order to purify and characterize the enzyme's protomers; (c) to determine the number of catalytic subunits of the native*

Principal Investigator	Title of Study	Abstract
		enzyme, and whether all subunits are identical or not, through cross-linking experiments on the native and the mercurial-modified enzyme; and (d) to establish the relation of enzyme's subunit composition to its transport function by measuring Na plus, K ions-fluxes in resealed red cell membranes in which some of the enzyme subunits have been cross-linked. The long-range goals of this project are: 1. Understanding of the mechanism of the active transports of Na plus and K ions across the cell membrane. 2. Elucidation of the mechanisms of molecular and cellular effects of a group of environmental hazards; namely, the short-chain alkylmercury compounds. *The general aim of this project is to elucidate the mechanism of action of cardiac glycosides at the cellular and the molecular levels. Since there is increasing evidence that the Na ion, K ion-ATPase complex of the cell membrane is the receptor for the toxic and the therapeutic effects of cardiac glycosides, our attention is focused on the interactions of these drugs with this enzyme complex. The specific research projects are as follows: Kinetics of interaction of cardiac glycosides with the Na ion, K ion-ATPase of intact cells and tissue will be studied. The intact human red cell will be used as a first model for such studies. These cells will be exposed, in vitro, to commonly used cardiac glycosides (ouabain, digoxin and digitoxin), and the rate of inhibition of the enzyme intact cells will be determined. The effects of various extracellular ligands of physiologic and pharmacologic importance (e.g., Na ion, K ion, Mg2 ion, Ca2 ion, pH, inorganic phosphate, and several drugs on the kinetics of inhibition of the enzyme of the intact cell) will be studied. The intracellular environment of the intact cell will also be altered, and the effects of these alterations on the rate of inhibition of the enzyme will be studied. Similar experiments will be performed to determine the influence of extracellular and intracellular environments on the rate of regeneration of the enzyme of the intact cell. The possibility that the enzyme of the intact red cell may be inhibited in patients who are continuously exposed to therapeutic doses of these drugs will also be investigated. An attempt will be made to develop methods for the study of the kinetics of interaction of cardiac glycosides with the enzyme of intact heart. BIBLIOGRAPHIC REFERENCES: George R. Henderson and Amir Askari, "Transport ATPase: **Thimerosal** Inhibits the Na ion plus K ion-Dependent ATPase Activity Without Diminishing the Na ion-Dependent ATPase Activity" Biochem. Biophys. Res. Comm. 69, 499 (1976). W. Huang and A. Askari, "Sensitivities of Na ion, K ion-ATPase and K ion-Phosphatase Activities to Cardiac Glycosides" Fed. Proc. 35, 834 (1976).*
GASSET, ANTONIO University of Florida **Funding Cycle:** 1974 Start 1 Jan 1973 End 31 Dec 1975 **Funding ICD:** NEI **Grant Number:**	TERATOGENIC AND TOXIC EFFECTS OF OPHTHALMIC DRUGS	*Non-radioactive IDU (5-iodo-2'-deoxyuridine), while not teratogenic to rats, does produce foetal malformations in rabbits when administered topically to the eye in doses similar to those used clinically, 0.1 percent four times a day for twelve days. These malformations include exophthalmus and clubbing of the forelimbs. By contrast, F3TdR (trifluorothymidine), another highly effective anti-herpetic agent currently under investigation but not available for general use, was found not to be teratogenic to rabbits, even when given in concentrations ten-fold greater than the doses used to produce IDU teratogenicity. Under the conditions of this study, systemically or topically applied **Thimerosal** was found to have no teratogenic effect in rabbits and rats.*

Principal Investigator	Title of Study	Abstract
5R01EY001098-02		
HENDLEY, J University of Virginia at Charlottesville **Funding Cycle:** 1979 Start 15 Sept 1979 End 31 Aug 1982 **Funding ICD:** NIAID **Grant Number:** -01	MECHANISMS OF HUMAN IMMUNITY TO BORDETELLA PERTUSSIS	*The objective of this project is to clarify the mechanism(s) by which human immunity to Bordetella pertussis infection is mediated. Pertussis is a serious respiratory infection in infants and children. Control depends upon a* ***thimerosal****-treated, whole organism vaccine which is associated with adverse reactions and provides short-lived immunity. Progress in understanding the pathogenesis of this infection and its immunity has been slow because of the lack of an experimental model clearly applicable to humans. The specific aims of this project are to determine if B. pertussis organisms adhere selectively to ciliated cells of the human respiratory tract and to investigate the effect on adherence of serum, saliva, and nasal secretions from individuals with natural and vaccine-induced immunity. Interaction of organisms and suspensions of squamous and collagenase-dispersed ciliated tracheal mucosal cells will be studied to determine whether there is selective attachment to cilia. Adherence will be assayed by light and fluorescence microscopy. Exposure of organisms to fragments of human nasal polyp in organ culture will also allow determination of specific attachment to cilia. With the polyp fragments maintained in organ culture, the effect of infection on ciliary activity will be determined by direct observation. Serum, saliva, and nasal secretions will be obtained from children before and after pertussis immunizapion and from patients convalescent from clinical pertussis. The effect of these sera and secretions on attachment of organisms to human respiratory epithelial cells will be studied. Ultimately, this basic information may permit the rational design of a safer vaccine directed at the components of the organism important in clinical disease.*
SAWYER, L 2 Studies **Funding Cycle:** 1992 1991 **Funding ICD:** CBER/FDA **Grant Number:** 1Z01BF003008-02, 3	EFFECT OF PRESERVATIVES ON THE STABILITY OF INACTIVATED POLIOVIRUS VACCINE VARYING REACTIVITIES OF MONOCLONAL ANTIBODIES WITH THE SAME POLIO VACCINE	*We have developed a sensitive ELISA assay for measuring the potency of trivalent poliovirus vaccines using mouse monoclonal antibodies for antigen detection. During routine tests of IPV we found a vaccine lot the type 2 component of which tested very low with our standard reagent; but gave satisfactory values with another type 2 monoclonal antibody or rabbit polyclonal sera. We are collaborating with another laboratory as a separate research project to identify the site specificity of our monoclonal antibodies. We are in the process of trying to elucidate the cause for this apparent epitope specific change. We reviewed the literature for chemicals known to affect the potency of poliovirus. We examined the effect of* ***thimerosal*** *on the potency of IPV. Preparations were held at three temperatures 37, 25 and 4 degrees C for 2 weeks. The preparations were then tested for potency by ELISA at 2, 10, and 14 days. Vaccine preparations held at 37 and 4 degrees degrees C were inoculated into mice on day 14. We found that combinations of IPV and* ***thimerosal*** *held for 14 days resulted in a loss of potency when kept at 25 degrees C as well as 37 degrees C for poliovirus types 1 and 2. Poliovirus type 3 was less sensitive to* ***thimerosal*** *and lost potency when the vaccine was held at 37 degrees C only. This suggested that handling of vaccines with* ***thimerosal*** *is very important in terms of IPV potency. We observed that our standard type 2 monoclonal antibody appeared to be directed against an epitope that had undergone changes in the presence of* ***thimerosal****. The potency of the vaccine measured in vitro did not correlate with immunogenicity in mice. These findings have important implications for manufacturers of combination vaccines as they will need to consider the effect of each preservative on the antigens in the combination.*
HULL, DAVID	OPHTHALMIC	*Recent work has demonstrated that certain medications currently used in ophthalmology are capable of*

Principal Investigator	Title of Study	Abstract
Medical College of Georgia **Funding Cycle:** 1976 Start 1 Apr 1976 End 31 Mar 1978 **Funding ICD:** NEI **Grant Number:** 1R23EY001654-01	MEDICATIONS AND THE CORNEAL ENDOTHELIUM	*altering both the physiologic function and anatomic appearance of the corneal endothelium. The purpose of this investigation is to define the physiological changes produced in the corneal endothelium by several ophthalmic preparations during in vitro perfusion in the specular microscope. These studies will establish the toxic dose levels of the agent tested as well as dose response curves. Transmission and scanning electron microscopy will be utilized to define anatomical and ultrastructural changes in the endothelium and be correlated with the physiological changes. Compounds to be investigated include: the preservatives benzalkonium chloride, chlorobutanol and* ***thimerosal****, the cationic surfactant cetyl pyridinium chloride, the enzyme Brinolase, and antiviral agents adenine arabinoside and hypoxanthine arabinoside.*
STOJILKOVIC, S **Funding Cycle:** 1994 **Funding ICD:** NICHD **Grant Number:** 1Z01HD000195-01	INTRACELLULAR SIGNALING IN ENDOCRINE CELLS	*The mechanisms by which G protein-coupled and tyrosine kinase receptors control calcium signaling, and the physiological implications of such signaling, were investigated in several cell types. Three patterns of calcium signaling were observed: base-line oscillatory, with the frequency but not the amplitude of spiking controlled by agonist concentration; slow-oscillatory, with a constant frequency and variable amplitude of spiking; and non- oscillatory. The pattern of calcium signaling was not determined by the receptor subtype but by post-receptor events. Base-line calcium oscillations were initiated by injection of inositol trisphosphate (InsP3), as well as by exposure to compounds such as ionomycin, thapsigargin, and* ***thimerosal****. However, when the cytoplasmic oscillator was activated by these agents, it operated only at the basal rate of 5/min and its spiking frequency did not change with increasing drug concentrations, as commonly occurs in agonist-and InsP3-stimulated cells. In contrast, both types of oscillations were affected by the depletion of intra-luminal calcium and by changes in [Ca2+]i, but were not inhibited by ryanodine. The voltage-sensitive calcium entry pathway also affected InsP3- dependent calcium oscillations in excitable gonadotrophs. In agonist- and Insp3-stimulated cells, sustained calcium oscillations were extinguished by hyperpolarization after 3-15 min despite the availability of calcium in the extracellular medium. Single depolarizing pulses transiently restored the amplitude of the sustained spiking in a dihydropyridine- and extracellular calcium- sensitive manner. The responses to depolarization showed a marked dependence on membrane potential that was correlated with the steady-state inward calcium current. In addition, the repetitive application of brief depolarizing pulses modulated the frequency of agonist and InsP3-controlled spiking. These extrinsically driven and extracellular calcium-dependent oscillations were sensitive to the calcium-pump blocker, thapsigargin, but not to ryanodine. A mathematical model based on these experimental observations gave responses to a wide range of agonist oses, including the subthreshold responses, superthreshold base-line oscillatory response with frequency determined by [InsP3], biphasic oscillatory, and biphasic non-oscillatory response. The model also predicted the existence of non-receptor-mediated calcium oscillations. Calcium signaling is sufficient to trigger the expression of primary response genes (PROS) in several types of endocrine cells. In pituitary gonadotrophs, the protein kinase C- dependent induction of PROs was found to be modulated both positively and negatively by physiological changes in (Ca2+]i. Thus, the pattern of calcium signaling may represent an efficient mechanism for the control of gene expression in endocrine and other cell types.*

Appendix E

Thimerosal Content in Some U.S. Licensed Vaccines updated 09-30-99

Vaccine	Brand Name	Manufacturer	Thimerosal Concentration[1]	Mercury ug/0.5 ml
DTaP	Acel-Imune	Lederle Laboratories	.01%	25
	Tripedia	Pasteur Merieux Connaught	.01%	25
	Certiva	North American Vaccine	.01%	25
	Infanrix	SmithKline Beecham	0	0
DTwP	All Products		.01%	25
DT	All Products		.01%	25
Td	All Products		.01%	25
TT	All Products		.01%	25
DTwP-Hib	Tetramune	Lederle Laboratories	.01%	25
Hib	ActHIB	Pasteur Merieux Connaught	0	0
	TriHIBit	Pasteur Merieux Connaught	.01%	25
	HibTITER (multi-dose)	Lederle Laboratories	.01%	25
	HibTITER (single dose)	Lederle Laboratories	0	0
	Omni HIB	SmithKline Beecham	0	0
	PedvaxHIB liquid[2]	Merck	0	0
	COMVAX[3]	Merck	0	0
	ProHIBit[4]	Pasteur Merieux Connaught	.01%	25
Hepatitis B	Engerix-B	SmithKline Beecham	.005%	12.5
	Recombivax HB	Merck	.005%	12.5
NEW!	**Recombivax HB preservative free**	**Merck**	**0**	**0**
Hepatitis A	Havrix	SmithKline Beecham	0	0

Thimerosal Content in Some U.S. Licensed Vaccines updated 09-30-99

Vaccine	Brand Name	Manufacturer	Thimerosal Concentration[1]	Mercury ug/0.5 ml
	Vaqta	Merck	0	0
IPV	IPOL	Pasteur Merieux Connaught	0	0
OPV	Orimune	Lederle Laboratories	0	0
MMR	MMR-II	Merck	0	0
Varicella	Varivax	Merck	0	0
Rotavirus	Rotashield	Wyeth-Ayerst	0	0
Lyme	LYMErix	SmithKline Beecham	0	0
Influenza	All Products		.01%	25
Meningococcal	Menomune A, C, AC and A/C/Y/W-135	CLI	.01%	25
Pneumococcal	Pnu-Imune 23	Lederle Laboratories	.01%	25
	Pneumovax 23	Merck	0	0
Rabies	Rabies Vaccine Adsorbed	BioPort Corporation	.01%	25
	IMOVAX	Pasteur Merieux Connaught	0	0
	Rabavert	Chiron	0	0
Typhoid Fever	Typhim Vi	Pasteur Merieux Connaught	0	0
	Typhoid Ty21a	Vivotef Berna	0	0
	Typhoid vaccine	Wyeth-Ayerst	0	0
Yellow Fever	YF-Vax	Pasteur Merieux Connaught	0	0
Anthrax	Anthrax vaccine	BioPort Corporation	0	0

1. A concentration of 1:10,000 is equivalent to a 0.01% concentration. Thimerosal is approximately 50% Hg by weight. A 1:10,000 concentration contains 25 micrograms of Hg per 0.5 mL.

2. A previously marketed lyophilized preparation contained .05% thimerosal.

3. COMVAX is not approved for use under 6 weeks of age because of decreased response to the Hib component.

4. ProHIBit is recommended by the Academy only for children 12 months of age and older.

Appendix F

Thimerosal Content of the Routinely Recommended Pediatric Vaccines			
Vaccine	**Tradename (Manufacturer)***	**Thimerosal Status Concentration**(Mercury)**	**Approval Date for Thimerosal Free or Thimerosal - Preservative Free (Trace Thimerosal)*** Formulation**
DTaP	Infanrix (GSK)	Free	Never contained Thimerosal
	Daptacel (AP)	Free	Never contained Thimerosal
	Tripedia (AP)	Trace(≤0.3 µg Hg/0.5mL dose)	03/07/01
DTaP-HepB-IPV	Pediarix (GSK)	Trace (<0.0125 µg Hg/0.5mL dose)	Never contained more than a Trace of Thimerosal
Pneumococcal conjugate	Prevnar (WL)	Free	Never contained Thimerosal
Inactivated Poliovirus	IPOL (AP)	Free	Never contained Thimerosal
Varicella (chicken pox)	Varivax (M)	Free	Never contained Thimerosal
Mumps, measles, and rubella	M-M-R-II (M)	Free	Never contained Thimerosal
Hepatitis B	Recombivax HB (M)	Free	08/27/99
	Engerix B (GSK)	Trace (<0.5 µg Hg/0.5mL dose)**	03/28/00
Haemophilus influenzae type b conjugate (Hib)	ActHIB (AP)/OmniHIB (GSK)	Free	Never contained Thimerosal
	PedvaxHIB (M)	Free	08/99
	HibTITER (WL)	Free	Never contained Thimerosal
Hib/Hepatitis B combination	Comvax (M)	Free	Never contained Thimerosal
Influenza	Fluzone (AP)	0.01% (12.5 µg/0.25 mL dose)[2] 0.01% (25 µg/0.5 mL dose)[2]	
	Fluzone (AP) (Preservative Free)	Trace (≤1.0 µg Hg/0.5mL dose, ≤0.5 µg/0.25mL dose)[2]	09/04/02
	Fluvirin (Chiron/Evans)	0.01% (25 µg/0.5 mL dose)	
	Fluvirin (Chiron/Evans) (Preservative Free)	Trace (<1ug Hg/0.5mL dose)	09/28/01
Influenza, live	FluMist[3] (MedImmune)	Free	Never contained Thimerosal

* Manufacturer abbreviations: GSK = GlaxoSmithKline; WL = Wyeth Lederle; AP = Aventis Pasteur; M = Merck.
** Thimerosal is approximately 50% mercury (Hg) by weight. A 0.01% solution (1 part per 10,000) of thimerosal contains 50 µg of Hg per 1 mL dose or 25 µg of Hg per 0.5 mL dose.
*** The term "trace" has been taken in this context to mean 1 microgram of mercury per dose or less.
1 Discontinued marketing thimerosal preservative-containing multidose vials in March, 2003
2 Children 6 months old to less than 3 years of age receive a half-dose of vaccine, i.e., 0.25 mL; children 3 years of age and older receive 0.5 mL.
3 FluMist is not indicated for children less than 5 years of age.