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May 1st, 2006

Dear Dr. Lawler,

Safe Minds has received and reviewed several documents that were distributed in preparation for the upcoming May 6th meeting to discuss the feasibility of additional analyses of the Vaccine Safety Datalink (VSD) data in an effort to assess potential associations between receipt of thimerosal-containing vaccines (TCVs) and the subsequent development of autism. During our review of the meeting materials, several questions and suggestions have surfaced that we wanted to share with both the organizers and participants in hopes that past mistakes using the VSD will not be repeated so as to create the most valid and reliable study possible. The purpose for this communication is to outline our specific concerns.

Essentially, there are substantial concerns related to the validity of both the major predictor (thimerosal exposure) and response (autism). These concerns can be broadly categorized into four sections: VSD Database Limitations, Previous VSD Analyses, Potential for VSD Acceptance Issues and Recommendations. In addition, we felt it would also be beneficial for panel members to be briefed with regard to events that precipitated this meeting being requested by several members of Congress which is included below.

Additionally, the impetus for the upcoming meeting stems from the letter sent to Dr. Schwartz by several members of Congress on February 22, 2006. The Congressional letter specifically excludes CDC from assuming leadership roles. Based on the agenda we have concerns about the extent to which the Centers for Disease Control (CDC) are involved in the upcoming meeting, as well as planning and executing a future project.

I. Background Information On Previous VSD Studies

When FDA announced in July of 1999 that infants who received multiple vaccines preserved with thimerosal may have been exposed to mercury in excess of Federal Safety guidelines, the Center for Disease Control, National Immunization Program (NIP) decided to investigate the issue using the VSD database in an effort to determine if associations existed with regard to exposure to thimerosal containing vaccines and adverse neurological outcomes.

Based on information obtained by SafeMinds in a FOIA request, Dr. Verstraeten and his supervisors at the NIP developed, and later modified several times, a VSD study protocol which resulted in four separate datasets from February 2000 to November of 2003 all of which were designed to assess the impact of neurodevelopmental disorders (NDDs) in children. With each new generation of data, elevated and statistically significant risks were reduced and/or eliminated entirely. Prior to producing reports for each of the four “Generations” Dr. Verstraeten conducted an even earlier analysis of the issues in November and December of 1999. Although he never prepared a formal report on this work, statistical tables obtained by FOIA demonstrate large and statistically significant mercury exposure effects that in many cases exceeded the findings of later reports.

These “Generation Zero” analyses followed a straightforward methodology that was relatively unaffected by the biases and manipulations of the dataset applied in subsequent analyses and are believed to be 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 reduced 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-based 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 compared to zero exposure groups ranged from low risks in the range of 1.5 to 2 to high risks in the range of 11 times the risk. The strongest effects occurred very early in life and at the highest levels of mercury exposure; consistent with infant brain development which is most sensitive to the earliest exposures. The elevated risk of autism for the highest exposure levels at one month of age ranged from 7.6 to 11.4 times that for zero exposure levels.

The difference in these results, as compared to later reports, reveal a number of methodological choices that may have been sources of systematic bias in later publications. Of particular concern is the decision to exclude children with less than two polio vaccines but retain all others. The children with less than two polio vaccines may not have been fully immunized and would have been more likely to have been in the zero exposure group. On the other hand, children with two polio vaccines but with low reported mercury exposures would be more likely to have exposure recording errors. The elimination of zero exposure categories (which served as the reference category for the

risk assessment) as well as elimination from consideration exposures in the very highest category had the effect of reducing dispersion in the data by truncating high and low exposures diminishing the ability to discern signal from noise.

Even with alteration in the inclusion criteria, strong dose-dependant associations between thimerosal exposure and several adverse neurological outcomes remained as described in one email from Dr. Verstraeten to his colleagues dated 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.”

A “draft” report of the data was ultimately generated by Dr. Verstraeten in February 2000. In spite of alterations to the inclusion criteria, highly significant and dose-dependant relationships persisted for ADD/ADHD, speech and language delays, and NDDs, in general. Please note that the relative risk of autism in infants 3 months of age who had received greater than 62.5 mcg of ethyl mercury decreased to 2.48. In the report, Dr. Verstraeten states, “In conclusion, we can state that this analysis does not rule out that receipt of thimerosal containing vaccines in children under three months of age may be related to an increase risk of neurological developmental disorders. Specific conditions that warrant a more detailed study include autism, dyslalia, misery and unhappiness disorder and attention deficit disorder.” To view this report see <http://www.safeminds.org/legislation/foia/ThimerosalVSDstudy001.pdf>

As a result of these findings CDC called a private meeting at Simpsonwood Conference Center in Atlanta where Dr. Verstraeten presented his findings to a small group of CDC and HHS officials, outside experts and vaccine manufacturers. The Simpsonwood meeting, ostensibly held to carefully review the CDC’s analysis on the impact of TCVs on child development, instead became a vehicle for making numerous deliberate choices that took positive findings in a single direction -- towards insignificance. Transcribed minutes to this meeting included in an appendix to this document outline several alterations to the original study design that had the net effect of lowering the number of adverse outcomes in the database and reducing the statistical significance of the relationship between those outcomes and exposure to thimerosal. To view the transcribed minutes to this meeting see [http://www.safeminds.org/legislation/foia/Simpsonwood Transcript.pdf](http://www.safeminds.org/legislation/foia/Simpsonwood_Transcript.pdf)

For example, Dr. Rhodes, a CDC statistician, 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 adverse outcomes in this group of children, of course, created variability in the data’s dependent variable making it possible

to establish statistical significance. Page 104: (Please see the attached appendix for actual quotes taken from the minutes of the Simpsonwood meeting) At the same time, he made arguments to exclude some cases that had unusually high thimerosal exposures and adverse outcomes. Any high exposure, high outcome group helped to produce a discernable signal in the data. Page 105: Additionally, he recommended including infants previously excluded because of either congenital or birth disorders. These additions would serve to add “noise” which could obscure the signal. Page 107

In their words and actions, the CDC demonstrates a clear bias against reporting positive results and made numerous deliberate choices that took positive findings in a single direction -- towards insignificance. Dr. Verstraeten sums up this concern in an email with regard to the Simpsonwood meeting discussions, “I feel we should use sound scientific argument and not let our standards be dictated by our desire to disprove an unpleasant theory.” For a detailed discussion on the four reported generations of VSD data, please see the attached PowerPoint presentations titled *SafeMinds Generation Zero* and *VSD SafeMinds Critique*.

II. Problems Identified In The VSD Database

A. Inability to Link Child and Maternal Records?

According to Dr. Verstraeten, the VSD dataset used for the thimerosal investigation could not be linked to maternal records. This structural impediment, if indeed true, limits the ability of a VSD to discern a link between total thimerosal exposure from products administered during pregnancy and adverse neurological outcomes. For example, Rho-D immune globulin products are routinely administered to approximately 15% of all pregnant women. Exposure to these products increased dramatically in 1991 when the American Academy of Obstetricians and Gynecologists recommended the addition of a prophylactic dose of RhoD immune globulin products to all rhesus (RH)- pregnant women during routine obstetric care at 28-weeks gestation. This recommendation was made in addition to the routine guidelines that RH- mothers receive RhoD immune globulins at any time during the pregnancy when the potential exists for maternal exposure to fetal blood, including invasive procedures like amniocentesis and villa sampling, or in the event of vaginal bleeding. With advancing technology, invasive diagnostic procedures during pregnancy have become more common. Exposure to mercury during pregnancy is known to result in a higher percentage of the exposure being transmitted to the fetus and an increase in neurological outcomes have been documented. Increasing exposure to thimerosal in the pre-natal period occurred at the same time that post-natal vaccine-based exposures increased with the introduction of HiB vaccine in 1988 and Hepatitis B vaccine in 1991. The chart below contains information regarding

Rho-D products available in the 1990's.

Thimerosal Containing Rho-D Immune Globulin Products			
<u>Product name</u>	<u>% concentration</u>	<u>Hg/ml.</u>	<u>average dose</u>
RhoGAM	0.003	15 mcg/ml	0.6 to 1 ml
Gamulin	0.01	50 mcg/ml	1- 2 ml
BayRho-D	0.01	50 mcg/ml	1 ml

In an investigation by Holmes (2003), demographic data was collected on children with autism. In this study, 43 out of 94 (46%) of the mothers of children with autism had received Rho-D products during the pregnancy compared to only 4 out of 34 (12%) of the control mothers ($p < 0.0002$). Several of the mothers of autistic children received multiple doses of Rho-D products. The mean number of Rho D immunoglobulin exposures per child in the autistic group was 0.52 compared to 0.12 in the control group. According to the American Red Cross, the incidence of RH- blood in the general population is 15%.

This observation is supported by a similar finding of elevated Rh incompatibility in mothers of autistic children in an article published in *Pediatrics* (2001) by Juul-Dam titled, Prenatal, perinatal and neonatal factors in autism, pervasive developmental disorders and the general population. Juul-Dam found that rhesus incompatibility occurred at significantly higher rates in autistic children than controls.

In addition to Rho-D thimerosal exposure, the CDC also stepped up its campaign of administering influenza vaccine to pregnant women after the first trimester in the past several years to the point that this is now a recommendation in routine obstetric care guidelines. Until 2003, all flu vaccine administered to pregnant women contained thimerosal and the CDC still does not state a preference for thimerosal-free vaccines for pregnant women.

In contrast to Dr. Verstraeten's statement that they were not able to link to maternal records is an exclusion criteria found in the February 2000 VSD study that excluded infants whose mothers had received Hepatitis B immune globulin products. This criteria excluded 192 infants from the analysis. We assume this criteria was added due to the fact that Hepatitis B immune globulin products also contained thimerosal.

B. Inaccurate Thimerosal Exposure Levels

According to early presentations made by Dr. Verstraeten, the birth dose of Hepatitis B may have been missed in as many as 3.8% of cases at NCK and 16.5% of cases at GHC. The birth dose of Hepatitis B was assumed to be missing if the child had received only 2 doses of Hepatitis B by the age of 2 years but had received all 4 DPT and HiB vaccines plus 3 polio vaccines.

A similar problem surfaced using VSD data for follow-up neurodevelopmental studies where HiB vaccine exposure level data contained inaccuracies because the same product actually had two formulations -- one contained 25 mcg of thimerosal and the other contained 50 mcg. Since the name of the product was the same, the only way to determine thimerosal exposure was to use the lot number and request thimerosal content information from the FDA which was not done when the data were collected and entered.

C. Non-HMO Specialist Diagnoses Missing from VSD Database

According to Dr. Verstraeten, if a child is referred outside the HMO to a specialist for an evaluation, the diagnosis obtained outside the HMO will not necessarily be reflected in the HMO database transmitted to the CDC. Therefore, it will be difficult to ascertain the true prevalence of NDDs in this population which creates a major limitation of the data. This is especially true given the fact that chart audits, discussed later in this document, required confirmation by a specialist to be included in the database and was one of the criteria used in analyzing the data.

III. Problems Identified In Previous VSD Data Analyses

A. Overall Young Age Of The Cohort

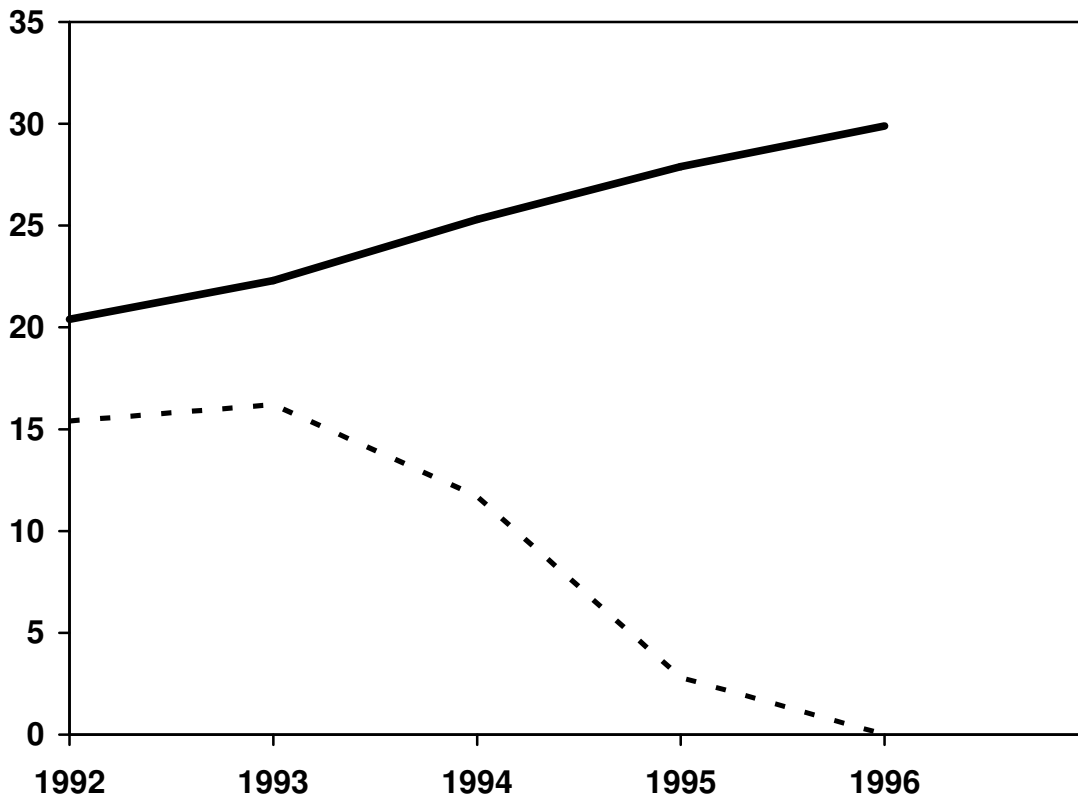
The chart below depicts the ages of children in the published study: Safety of thimerosal containing vaccines: a two phased study of computerized HMO database, *Pediatrics* (2003). This information was not included in the published document but was obtained through a Congressional request.

<u>HMO</u>	<u>UNDER AGE 3</u>	<u>UNDER AGE 4</u>	<u>UNDER AGE 5</u>
HMO-A	32%	46%	58%
HMO-B	26%	42%	56%
HMO-C	40%	56%	71%

Considering that the average age for the diagnosis of autism in the VSD database was 44 to 49, it is clear that at least 40% of children in the database were too young to be diagnosed with autism. Numerous CDC officials who worked on the investigation have acknowledged this major shortcoming. Dr. Verstraeten, the lead author of the study, stated in his presentation of VSD findings at Simpsonwood in 2000, pg. 42. “But one thing that is for sure, there is certainly an under-ascertainment of all of these because some of the children are just not old enough to be diagnosed. So the crude incidence rates are probably much lower than what you would expect because the cohort is still very young.”

B. Known California Rates of Autism vs. VSD Autism Rates

The graph below show pictorially the concerns related to ascertainment of cases of autism in the VSD dataset. The dotted line reflects VSD autism rates and the solid line reflects California rates. The vertical axis is rates of autism per 10,000.



Sources: VSD analysis 2-29-00 and the California DDS data.

The concerns about inclusion of only children who are of sufficient age to have experienced the outcome, are supported by an internal CDC email from Dr. Colleen Boyle, Assistant Director for Science in the Division of Birth Defects at CDC who reviewed the early VSD findings dated April 25th, 2000. Dr. Boyle noted that in addition to autism, the rates for ADHD and language delays are also under reported in the data and she states, “Since most of these diagnoses are not picked up until the second or third year of life have you considered eligibility criteria of at least 18 months or two years?” She goes on to state that the “big issue is the missed cases. Clearly there is a gross underreporting-- 1.4% of kids dx’ed with a speech and language problem vs. 4-5% from reported national surveys; <1% with ADHD vs. 3-10% reported previously; etc.” Clearly, if the outcome is not in the dataset, its relationship with the predictor cannot be evaluated.

C. Chart Audits Resulting in Reclassifications of Outcomes

In his VSD presentation to IOM in 2001, Dr. Verstraeten reported that a chart audit was performed on all cases of speech and language delay, ADD and autism to confirm the diagnosis. The need for this additional audit is perplexing in that Dr. Davis reported at Simpsonwood pg. 88, “Now one might imagine that [relative risk of 1.018] would just disappear once we actually confirmed these diagnoses from chart review, but in fact it did not. You see if the diagnosis was mentioned in the chart, the relative risk increases ever so slightly.”

Unlike the first chart audit process, where CDC ascertained that the electronic client records matched the actual chart records, the second audit actually resulted in a reclassification of diagnoses made by primary care providers. All charts in the VSD database that contained the outcomes ADD, speech delay and autism were pulled and audited by ancillary clinic staff. The diagnosis that appeared in the clinic record made by the pediatrician would only be accepted if the child’s chart also contained a written report from a behavioral specialist who confirmed the diagnosis. As mentioned earlier, no mechanism was in place to track a child referred to a clinic outside the HMO for evaluation and outside diagnostic data were not necessarily recorded in the HMO record.

The audit process resulted in only 40% of the cases of ADD, 50% of the cases diagnosed with speech delay and 80% of the cases of autism accepted as being confirmed in the chart. (Please refer to pages 89 through 91 of the IOM transcribed meeting minutes 7-16-01 “Thimerosal-Containing Vaccines and Neurodevelopmental Outcomes.”) The results

of this reclassification of outcomes again significantly affected the reliability and validity of the study's outcome variables which in turn, affected the analysis and findings.

<u>VSD Chart Audit - % Removed from analysis</u>		
ADD	Speech Delay	Autism
60%	50%	20%

D. Collapsing Of Thimerosal Exposure Level Data

In the original analyses of the data in 2000 by Dr. Verstraeten, the thimerosal exposure levels were broken down into 12.5 mcg. increments. In the published version of the VSD investigation, exposure categories were collapsed into just three categories:

<u>MERCURY EXPOSURE BY 7 MONTHS OF AGE</u>		
Low Exposure	Medium Exposure	High Exposure
0 - 75	87 - 162.5	> = 175

Collapsing the categories into 3 broad ranges of exposure, transforms an interval variable into a categorical variable, greatly impairing the sensitivity of analyses that can be performed. Moreover, the effects exposure levels early in life, when neurologic health is believed to be most at risk, are virtually eliminated creating a large category which makes the analysis difficult, if not impossible. Data that is available in 12.5 mcg increments is more likely to show dose-response effects as were found in the earlier Verstraeten analyses.

E. Purchase and Addition of Data to the VSD Dataset

To further investigate VSD findings, CDC purchased an additional HMO database, Harvard Pilgrim. This database contained 30,000 subjects and was reduced by half, 16,646 subjects. The only outcomes that were investigated were those previously determined to be significant which included tics, ADD, speech delay, language delay and unspecified delay. Apparently, the sample size was only large enough to investigate

ADD and speech delays. Only speech delay at 3 months of age was significantly related to thimerosal exposure.

The ability to perform proper evaluations depends on access to good data. It is general knowledge that Harvard Pilgrim has been under severe financial constraints related to internal problems with its “information systems.” These financial hardships resulted in Harvard Pilgrim being placed under state receivership in March 2000. One must question if the problems with their information systems could impact the VSD database analysis collected at this HMO. Therefore, the continued use of this dataset defined as HMO-C should be evaluated with caution.

F. Disaggregation of HMO Data

For reasons that have never been satisfactorily explained, a large dataset containing information from all three HMOs NCK, GHC and Harvard-Pilgrim was disaggregated into smaller HMO-specific datasets delineated as HMO-A, HMO-B and HMO-C. As a result, the power to detect statistically significant relationships was substantially eroded due to the reduction in sample size.

G. Over stratification of VSD Data

The additional levels of data stratification by gender, year and month of birth plus an additional stratification by clinic added after the 2001 IOM presentation along with adjustments for health care seeking behaviors make it highly unlikely that the analysis would have the power to detect statistically significant relationships. This is a common problem for investigators working in multivariate environments. Considering all the other issues with this database, the lack of a solid a priori theoretical basis for addition of specific covariates and controls, the analyses were likely to be under-powered. Interestingly, Dr. Verstraeten even warns about the hazards of constructing such models in an article published in *Expert Review of Vaccines* (2003), Vaccine safety surveillance using large linked databases: Opportunities, hazards and proposed guidelines. “Any pharmaco-epidemiologist working on large linked databases will soon be tempted to construct models with multiple stratification and covariates in an effort to adjust for every possible confounder available” (pg. 23).

H. “Disenrollment” After First Diagnosis

According to the VSD study protocol, the endpoints for inclusion in the study included which ever of the following that occurred first: “the date of first diagnosis, the date of first disenrollment from the HMO or the last possible day for the follow-up period.” This has been interpreted to mean that once a diagnosis such as speech delay was made, the

child was removed from the database. Therefore, a subsequent diagnosis would not be included. Using this criteria would result in an under-reporting of diagnoses such as autism, which often initially present as a speech or language delay or general neurodevelopmental delay.

IV. Potential For VSD Findings Not To Be Broadly Accepted

A. Static vs. Dynamic Files

According to our understanding of the VSD database, the CDC receives raw data annually via tapes sent from the participating HMOs. The CDC then cleans, edits and merges the data from the HMOs into one master file which are collected in annual cycles. A key issue that must be resolved is whether CDC files are static or are dynamic. Static files are those that remain unchanged over time. They are updated or corrected by supplements. Dynamic files, on the other hand, can be overwritten where new or edited information is inserted. Therefore, it is very difficult, if not impossible, to replicate earlier VSD investigations with dynamic files.

B. CDC's Involvement in the Review Process

The CDC's NIP is tasked with promoting vaccines and ensuring high vaccination rates in addition to monitoring vaccine safety. Unfavorable vaccine safety reports lead to lower vaccination rates. This situation creates a built-in conflict of interest that is likely to create a bias with regard to investigating vaccine safety issues. Therefore, any CDC involvement in this process will not be well received. Senator Lieberman made it very clear in his letter to NIEHS that "If the federal government is to have a study whose results will be broadly accepted, such a study can not be led by the CDC." To that end, use of data files from the CDC that are dynamic, where there is an opportunity for the datasets to be edited will be viewed with a great deal of concern. Additionally, CDC involvement in the planning stages of this analytic process will not be received as independent by the public.

V. Recommendations

1. Increase Public Trust Through Participation and Oversight.

Ensure that the project design, implementation, analysis and oversight processes are fair and open to the public. All committees should include strong and meaningful representation from the public and autism community at all project phases.

Ensure that establishing the charge, research design and methods, conducting the analyses, interpreting results and writing the final report are performed by independent outside investigators without the direction of CDC.

2. Ensure that VSD Data is Reliable and Valid

A complete dataset will contain child records linked to maternal records. Data shall contain all prenatal thimerosal exposures including Hepatitis B immune globulin products, Rho-D immune globulins, influenza, tetanus and other vaccines. In addition, chart audits (both maternal and child) should be performed by independent investigators to ensure that exposure data is accurate. This process may require consultation with the FDA to ascertain exposure level by lot number.

Thimerosal exposures should capture all exposure levels including prenatal experiences. Actual interval-level exposure data should not be collapsed into categorical formats thereby affecting the ability to discern relationships to outcome states.

Additionally, the dataset should contain two groups of zero dose exposures: vaccinated children who did not receive any thimerosal-containing vaccines and completely unvaccinated children as requested by the Congress.

The dataset and all additional ad hoc analyses should be based on static files

3. Ensure that Analyses are Powered to Detect Statistically Significant Relationships

HMO data should not be disaggregated to perform separate analyses. Ensure that children in the dataset are at least four years of age and beyond a reasonable age of ascertainment for an autism diagnosis.

4. The Analyses Should Detect All True Relationships

High thimerosal exposure levels should be compared to low exposure levels and to unvaccinated children. The effects of prenatal exposures should be evaluated as part of total thimerosal exposures. Additionally, these exposures should be parsed out for separate analyses so that the differential effect of prenatal use of thimerosal-containing products can be discerned.

References

Holmes, A.S. et. al. Reduced levels of mercury in first baby haircuts of autistic children. Int. J. of Toxicol. 2003 Jul-Aug; 22(4):277-85.



Juul-Dam, N. et. al. Prenatal, perinatal and neonatal factors in autism, pervasive developmental disorders and the general population. *Pediatrics*. 2001, Apr; 107 (4) :E63.

Verstraeten, T. et al. Vaccine safety surveillance using large linked databases: Opportunities, hazards and proposed guidelines. *Expert Rev. of Vaccines*. 2003, Feb; 2 (1): 21-29
Verstraete, Pediatrics

Verstraeten, T. et al. Safety of thimerosal-containing vaccines: A two phased study of computerized health maintenance organization databases. *Pediatrics*. 2003 Nov;112(5):1039-48.

Sincerely,

Lyn Redwood

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President, SafeMinds

Vicky Debold

Vicky Debold, RN, PhD
Director, SafeMinds

cc.

Senator Joseph Lieberman
Congressman Dave Weldon
Congressman Carolyn Maloney
Congressman Chris Smith
Senator Debbie Stabenow
Congressman Dan Burton
Congressman Maurice Hinchey
Dr. David Schwartz

Appendix of quotes

Dr. Rhodes, pg.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, then in a sense we really don’t need them.”*

Dr. Rhodes, pg. 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.*

Dr. Rhodes, pg 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.”*