August 31, 2007

U.S. Department of Health and Human Services
Office of Research Integrity
1101 Wootton Parkway, Suite 750
Rockville, Maryland 20852

Via: Hand delivery: John E. Dahlberg, PhD and Lynda Youngman

Re: Verstraeten, T, Davis, RL, DeStefano F, et. al. Safety of thimerosal containing vaccines: a two phased study of computerized health maintenance organizations databases. *Pediatrics* 2003; 112: 1039-1048

Issue

In 2004 SafeMinds (Sensible Action For Ending Mercury Induced Neurological Disorders) reviewed the above referenced article and voiced concerns regarding data analysis and related conclusions put forth in this investigation in a letter to the editor of the journal *Pediatrics* and to the "Post Publication Peer Review" (P3R) website. At that time we called for an external audit of the research ethics and supervisory protocols involved in preparing sequential versions of the Vaccine Safety Database (VSD) for public review and ultimate publication. (*Link to Exhibit 1*). We did not receive a response to our request. Since this time additional concerns have come to light which call into question the study's conclusion of "no consistent significant associations between thimerosal containing vaccines (TCVs) and neurodevelopmental outcomes". These concerns include:

- A recently released report from the Department of Health and Human Services in October of 2006 which identified several inherent weaknesses in the ability of the Vaccine Safety Database utilized in the Verstraeten study which reduces the ability of the database to identify associations between thimerosal exposure and adverse neurological outcomes like autism.
- Alterations in the entrance criteria and study design protocols were made after viewing initial findings and not reported in the published version of the investigation. The

study authors were well aware that these alterations would result in a decrease in statistical significance and in some instances, findings to disappear entirely.

- Datasets used in the study were disaggregated which reduced the power to detect associations which were only found when the datasets were combined. One of the study authors acknowledged that the data must be combined to have the power to detect associations, although in the final published versions of the study after this acknowledgement, the HMO's were disaggregated.
- Conflicts of interest were not divulged in the publication of the article. The lead author of the investigation was employed by a vaccine manufacturer and another author who previously acknowledged receiving funding and consulting fees from vaccine manufacturers did not acknowledge any funding conflicts.

It is our opinion that the above mentioned concerns represent a pervasive pattern of bias and conscious manipulations of samples and statistics in order to produce a negative finding regarding the dangers of thimerosal exposure in infants and children. In addition, these series of events, including the suppression and falsification of data, represent scientific misconduct deserving of a full review by the Office of Research Integrity.

1. Database utilized for the investigation is fraught with inherent weakness

In light of these above referenced concerns we would like to draw your attention to a recently report released by the Department of Health and Human Services (HHS) National Institutes of Health titled *Thimerosal Exposure in Pediatric Vaccines*. This report is a result of a congressional inquiry regarding the feasibility of using the Vaccine Safety Datalink (VSD) database to conduct an investigation into the rates of autism before and after removal of thimerosal from infant vaccines. SafeMinds again voiced our concerns related to the validity of both the major predictor (thimerosal exposure) and response (autism) broadly categorized into VSD database limitations and previous VSD analyses to members of the expert panel. *(Link to Exhibit 2)*

The NIH report identified several serious problems that were "judged to reduce the usefulness of an ecologic study design using the VSD to address the potential association between thimerosal and the risk of AD/ASD". These include: *uncertainties in case ascertainment, heterogeneity of business practices within and across managed care organizations (MCOs) and their systematic changes over time, the inability to control for temporal changes in awareness and diagnostic practices and potential confounding factors including the inability of the database to link with maternal records.* The panel concluded that the cumulative effect of these inherent weaknesses reduced the usefulness of the VSD database for addressing the potential association between the vaccine preservative thimerosal and the risk of autism spectrum disorders. *(Link to Exhibit 3)*

It is our understanding that the Verstraeten article was submitted to the journal *Epidemiology* and was not accepted for publication prior to its submission to Pediatrics. One must wonder if during

the peer review process the inherent weakness of the VSD database identified by the NIH expert panel were acknowledged, resulting in the rejection.

2. Alterations in the study protocol and design after viewing findings not divulged in the publication

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 by changes in the study design protocol, alterations in entrance criteria and statistical methods based on FOIA documents and transcribed minutes to private meetings. 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 groups. 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. 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.* *(Link to Exhibit #4)*

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." (*Link to Exhibit #5*)

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 less than 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." *(Link to Exhibit #6)*

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 of this meeting 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. A detailed summary of the events that took place at the Simpsonwood meeting along with verbatim quotes from invited participants was prepared by SafeMinds. *(Link to Exhibit #7)*

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 the case of Raphael B. Stricker, D.[http://grants.nih.gov/grants/guide/notice-files/not93-177.html], for instance, the [[United States Office of Research Integrity |U.S. Office of Research Integrity]] has found the removal of samples from a [[data set]] in order to reach a desired conclusion to be grounds for disbarment from funding.

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." *(Link to Exhibit 8)*

3. Acknowledgment that the published investigation lacked power to detect associations by one of the studies authors

A basic premise of scientific research is the fact that the larger the number of participants in an investigation, the more robust and accurate the 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. In the publication the authors never mention the earlier runs of the data where the datasets had been combined which resulted in several statistically significant findings. As a result of the disaggregation of the data the power to detect statistically significant relationships was substantially eroded due to the reduction in sample size. This concern was recently supported by an expert reanalysis of the VSD thimerosal screening analysis Harland Austin, Dsc and Cathy Lally, MSPH as part of a discovery order filed in the United States Court of Federal Claims in December of 2006. The experts, as part of this reanalysis combined data from HMO-A and HMO-B which resulted in statistically significant finding for tics and sleep disorders which was not reported in the published data. With the combined data from all three HMO's, the P values became appreciable smaller which provides stronger statistical evidence that these positive findings; language delay, tics and sleep disorders, are not due simply to chance. (*Link to Exhibit 9*)

In fact, one of the study authors, Robert L. Davis acknowledges in an email communication to Frank DeStefano, an employee of the CDC's National Immunization Program and co-author of the study in question on June 26th 2000 that they needed to be careful in their analysis of the Harvard-Pilgrim data (HMO-C) "since the main question will be whether or not it (HMO-C) had adequate power to detect an association that was only found when we lumped GHC and NCK together." Obviously, the study authors were aware that the decision to segregate the datasets would result in a lack of consistent significant associations as reported in their investigation published in November, 2003. This purposefully manipulation represents scientific misconduct and falsification of data. *(Link to Exhibit 10)*

4. Conflicts of interest were not divulged

In addition to these serious limitations of the VSD database in investigating an ecological link between exposure to TCVs and autism, we would like to also point out numerous conflicts of interest that were not disclosed in the publication of the article. These include the fact that Dr. Verstraeten, lead author of the investigation, was employed by the vaccine manufacturer GlaxoSmithKline (GSK) beginning July 16, 2001, a full two years prior to publication of the article. The 2003 published version of the VSD investigation is much different from the data presented by Dr. Verstraeten at the Institute of Medicine meeting in 2001 which confirms the fact that the study design, evaluation and conclusions continued to undergo transformation after Dr. Verstraeten's employment with GSK.

The second author, Dr. Robert L. Davis disclosed to JAMA in 2000 that he had received funding and consulting fees from Merck and SmithKline Beecham, both manufacturers of thimerosal containing vaccines. Again, these conflicts were not disclosed. Merck and SKB, now GlaxoSmithKline, have both been names as defendants in several legal cases involving their vaccine products Recombivax-HB and Engerix-B which contained thimerosal.

Three of the remaining authors were employees of the Centers for Disease Control and Prevention's (CDC) National Immunization Program (NIP). 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. In 2001 it was reported that the CDC held 28 licensing agreements with companies and one university for vaccines or vaccine-related products and had eight ongoing projects to collaborate on new vaccines which clearly places CDC in the vaccine business.

Conclusion

The Office of Research Integrity defines *Scientific misconduct* as the violation of the standard codes of scholarly conduct and ethical behavior in professional scientific research and *Falsification* as the manipulation of research materials, equipment or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.

A related issue concerns the deliberate suppression, failure to publish, or selective release of the findings of scientific studies. Such cases may not be strictly definable as scientific misconduct as the deliberate falsification of results is not present. However, in such cases the intent may nevertheless be to deliberately deceive. Studies may be suppressed or remain unpublished because the findings are perceived to undermine the commercial, political or other interests of the sponsoring agent or because they fail to support the ideological goals of the researcher.

We have grave concerns that the Verstraeten, et al publication of an investigation supported with federal funds represents scientific misconduct and includes falsification and manipulation of statistical methods in an effort to reach a desired result. And sound scientific principles, such as pooling of data, would result in additional associations not detected in the published version of the research. Therefore, we request a full review of this research by the Office of Research Integrity.

Respectfully submitted,

Lyn Redwood, RN, MSN
President, SafeMinds

Senator Joseph Lieberman
Senator Barack Obama
Congressman Dave Weldon, MD
Congressman Bart Gordon
Congressman Dan Burton