safeMinds
Sensible Action For Ending Mercury-Induced Neurological Disorders

February 16, 2004

Dr. Kathleen Stratton
Institute of Medicine
National Academy of Sciences
2101 Constitution Avenue, NW
Washington, DC 20418

Dear Dr. Stratton:

Safe Minds would like to thank-you and the members of the committee for holding the February 9th, 2004 meeting regarding vaccines and autism. Although there are a number of very exciting research findings in the last stages of completion that were not yet available for the committee's review, the information that was heard, especially the work presented by Drs. Horning, Haley, Bradstreet, and Baskin, lay the foundation in documenting an increased vulnerability in some children to mercury from vaccines.

The purpose of this letter is to comment on the Davis VSD presentation and ask that you please forward our concerns to all members of the committee. Our concerns relate to inherent inadequacies of this investigation which include: under ascertainment due to the young age, chart audits that resulted in adverse outcomes being reclassified, collapsing of the exposure categories, alteration of the entrance criteria, separating HMO's, adding additional levels of stratification of the data, controlling for health care seeking behaviors and removing combined categories of adverse outcomes such as neurodevelopmental disorders present in the earlier reports.

Overall young age of the cohort

During public comment, I asked Dr. Davis the age of the children in the VSD database used to assess thimerosal safety. He said he did not know the average age of the children, although he was quick to point out in reference to other investigations that age was critical in ascertaining outcomes. I have yet to receive a response to both my oral and written request for this information from CDC, but I was able to access the average age of the children in the published *Pediatrics* version of the VSD analysis through a congressional request, the results which appear below.

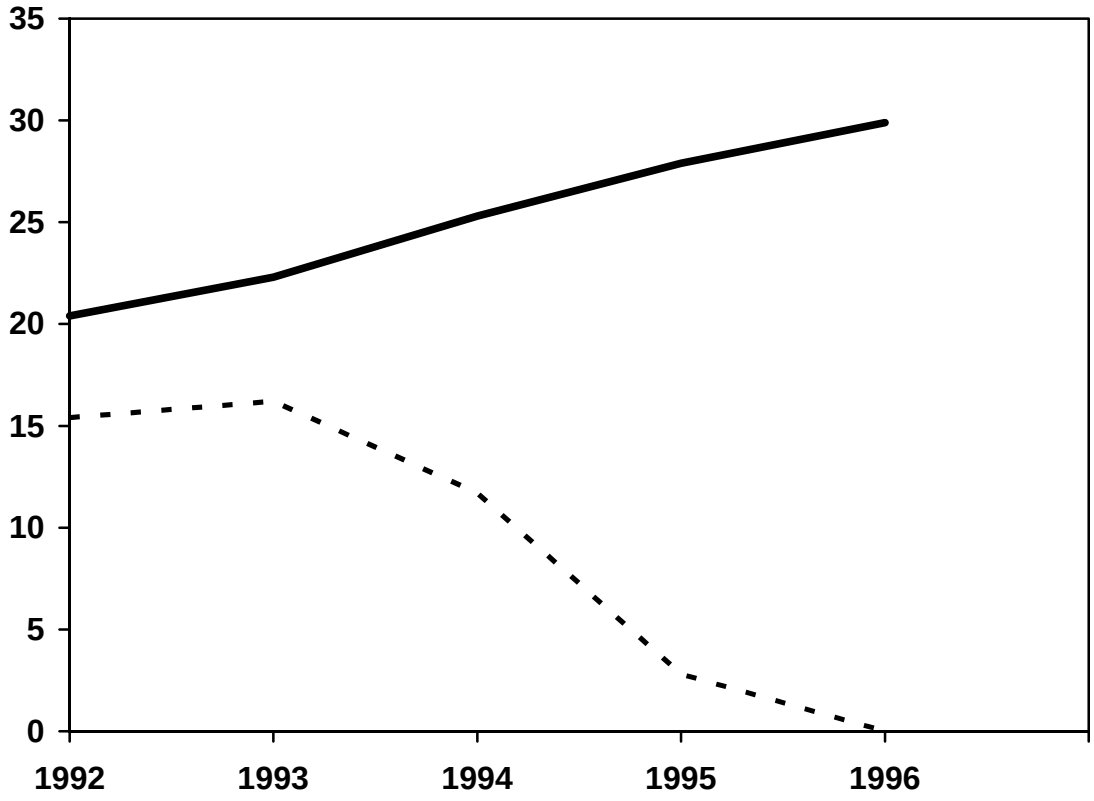
HMO	UNDER AGE 3	UNDER AGE 4	UNDER AGE 5
HMO-A	32%	46%	58%
HMO-B	26%	42%	56%
HMO-C	40%	56%	71%

Considering that the average age for the diagnosis of autism in the VSD database was 44 to 49 months it is easy to see that almost half of the children in the database were too young to be diagnosed. 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 the 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."

The *National Journal* (1-03-04 issue) reported that "a CDC official who helped write the study accepted the critics' charge that it contained many children too young to be diagnosed autistic. 'This is true,' said scientist Frank DeStefano." This concern is confirmed when you look at recent reports from the state of California which have estimated the rates of autism spectrum disorders to be as high as 1 in every 132 children (Granite Bay, Ca.) verses the rate of 1 in 550 found in the California dataset from HMO B.

Known California vs. VSD (2-29-00) Autism Rates

(note only VSD data available for autism rates per year) Vertical= Rates of autism per 10,000
Solid line = known California rates. Dotted line = VSD rates of autism.



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

Chart audits resulting in reclassifications of outcomes

In 2001 Dr. Verstraeten reported that a chart audit was preformed on all cases of speech and language delay, ADD and autism to confirm the diagnosis in his presentation of the data to IOM. 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 records matched the actual chart records, the second audit 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 somewhere in the child's chart there appeared a written report from a behavioral specialist who confirmed the diagnosis. A problem with this approach is that there is no mechanism in place to track a child referred to a clinic outside the HMO for evaluation.

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 meeting 7-16-01 "Thimerosal-Containing Vaccines and Neurodevelopmental Outcomes.") The results of this reclassification of outcomes again significantly impacted the data analysis and findings by removing a majority of the outcomes.

VSD Chart Audit - % Removed from Analysis

ADD	Speech Delay	Autism
60%	50%	20%

Collapsing of data regarding exposure levels

Another concern is the collapsing of the exposure categories. In the original analyses of the data in 2000 by Verstraeten the exposure levels were broken down into 12.5 mcg. of mercury increments. In the Davis presentation the exposure categories at 7 months of age were collapsed into just three categories, shown below.

MERCURY EXPOSURE BY 7 MONTHS OF AGE

Low Exposure	Medium Exposure	High Exposure
0 - 75	87 - 162.5	> = 175

Collapsing the categories into 3 broad ranges of exposure levels takes away the significance of the low rate of outcomes in the 12.5 to 25 mcg exposure levels and the higher rate of outcomes as the dose gradually increases. Assessing the mercury exposure levels by 12.5 increments would make it easier to identify the dose response relationships found in the earlier Verstraeten analyses.

Alteration of the entrance criteria

In the initial reports of the VSD data infants were excluded who had either congenital or birth disorders. The reason for this exclusion was to have the cleanest possible data free of confounding variables. In later reports of the data the entrance criteria was altered allowing for inclusion of infants with congenital and birth disorders previously excluded. These infants are known to be at higher risk for adverse neurodevelopmental outcomes. The addition of these infants to the data created "noise" and resulted in an overall dilution of the findings. This assertion is documented by Dr Rhodes in the Simpsonwood minutes pg. 107 "Throwing them all back in...is going too far, but that further brings things down." Recipients of thimerosal containing hepatitis B immune globulin products had also been excluded in earlier analyses of the data but were included in the *Pediatrics* published version of the data.

Separating HMO databases and adding additional stratification by HMO clinics

In the earlier reports by Verstraeten the data collected from HMO-A and HMO-B were combined which resulted in a larger overall population available for analysis and greater likelihood of identifying at least 50 cases which was a requirement of the investigation. Later versions of the investigation separated out each individual HMO which reduced the statistical power of all the analyses. The investigators used HMO C to verify the findings of HMO-A and HMO-B which provides a rationale for not combining HMO C with the other two HMO's, but there is no reason not to combine the findings from HMO- A and B.

Controlling for health care seeking behaviors

One of the biggest differences in the *Pediatrics* version of the VSD data in comparison to earlier reports is the attempt to control for health care seeking behaviors by using the Cox proportional hazards model. This requirement for HMO's A and B restricted the analysis of case children to children who made at least one visit to a clinic or emergency department at the same month of age as cases published report. This requirement drastically reduces the size of the comparison group for cases. It also favored the inclusion as controls children attending clinics often resulting in an over sampling of "sick" children which are not an ideal comparison group. The resulting bias would mask any adverse effect of thimerosal on the disorders.

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Removing combined categories from analysis

In the more recent published report, the CDC investigators did not analyze combined categories for neurologic degenerative and neurodevelopmental disorders as they had done previously. Some of these findings were statistically significant in the earlier report, including the entire category of neurodevelopmental delays in general. One must question the rationale for not evaluating the overall categories in the published paper.

In summary

When you add up the problems of under-ascertainment of the dataset due to the young age of the VSD participants, the reclassification of diagnoses, the collapsing of exposure categories and the addition of previously excluded clients into the database it becomes unlikely that the earlier findings of significance could survive such data adjustments.

The excessive levels of data stratification by gender, year and month of birth plus an additional level of stratification by clinic added after the 2001 IOM presentation along with adjustments for health care seeking behaviors further reduces the chances that the analysis would have sufficient power to reach statistical significance.

Dr. Verstraeten warns about the hazards of constructing such over stratified 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 LLDBs (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). The article refers to such approaches as "black box analyses." Unfortunately, Dr. Verstraeten's colleagues at CDC who made these alterations to the investigation after Dr. Verstraeten left CDC to work for Glaxo did not heed his warnings.

Further, in our investigation into the Thimerosal VSD analysis it was learned that the CDC had previously submitted the VSD thimerosal and adverse neurodevelopmental research to the *American Journal of Epidemiology* in December of 2002. The journal rejected the research for publication. We were told by CDC the reason for rejection was due to the fact that the study exceeded 4000 words, but a conversion of the *Pediatrics* HTML format to text, removing tables, references and credits, result in a 4109 word count.

Sincerely,

Lyn Redwood

Lyn Redwood RN, MSN
Pres. Safe Minds