Abt Associates Inc.

Infant Environmental Exposure to Thimerosal and Neuropsychological Outcomes at Ages 7 to 10 Years

Technical Report Volume I

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1. Executive Summary

The current study was conducted to investigate whether there are relationships between prenatal and/or early childhood exposure to thimerosal-containing vaccines and immune globulins and neurodevelopmental functioning at ages seven to ten years. The study utilized a retrospective cohort design wherein computerized medical records were used to select a sample of children who had been exposed to varying amounts of thimerosal-containing vaccines and immune globulins during infancy. The children were assessed at ages 7 to 10 years using a battery of neurodevelopmental assessments administered in a clinical setting. Results are based on data obtained from 1,047 study participants.

There are three major strengths of the study. The first is that we were are able to compute accurate measures of each child's prenatal and early childhood exposures to ethylmercury from thimerosal-containing vaccines and immune globulins. We used three sources of data on vaccination and immune globulin receipt to develop measures of exposure levels. The first source was computer-automated records maintained by the HMOs as part of the Vaccine Safety Datalink system and as part of their administrative record keeping systems. The second source was from detailed abstractions of medical charts of children and their mothers. These data were collected by a team of experienced chart abstractors. The third source was from personal records and responses to survey items provided by parents during a detailed interview with each child's biological mother.

The second major strength of the study was that outcomes were measured in a clinical setting using a battery of standardized assessment tools. Outcome measures spanned domains of speech and language, verbal memory, reading achievement, fine motor coordination, visual spatial ability, attention/executive functioning, behavior regulation, tics, and general intellectual functioning.

The third major strength of the study is that we were able to obtain detailed information for each child on potential confounding factors. These included data on other prenatal and early childhood exposures, on other diagnoses and medical conditions of children and their mothers, and on whole range of child and family characteristics. These included income, maternal education, birth order, plurality, family size/structure, language spoken in the home, maternal age, duration of breastfeeding, and maternal diagnoses of neuropsychological disorders. These data were obtained from parent interview, from medical record abstraction, and from the computer-automated records.

The primary weakness of the current study is that exposure levels were not determined in a randomized, controlled trial (RCT) design. Although the study measured and controlled for a wide range of potential confounders, it is impossible to know with certainty whether the threat of selection bias has been eliminated. Selection bias will have affected the results if one or more unmeasured factors have causal effects on both the amount of exposure that children receive, and on outcome measures. Given this important limitation of the design of the study, results can only be judged as informative, not conclusive. The study was intended to be an important contribution to a growing literature regarding the

possible effects of ethylmercury, and was not intended to be a definitive concluding statement of whether the ethylmercury in thimerosal-containing vaccines and immune globulins does or does not cause harm.

Associations between each of 42 outcome measures and exposure to thimerosal-containing vaccines and immune globulins were estimated from linear and logistic regression models that controlled for potential confounding effects of family demographics and other factors. Models were fit to each of the 42 outcome measures to estimate the effects of:

- Prenatal exposure;
- Neonatal exposure (cumulative exposure birth to one month);
- Birth to 7 months exposure (cumulative exposure birth to seven months);
- For males - Prenatal exposure;
- For males – Neontal exposure;
- For males – Birth to 7 months exposure;
- For females - Prenatal exposure;
- For females – Neontal exposure;
- For females – Birth to 7 months exposure;
- Interaction effects of prenatal exposure and cumulative exposure birth to seven months;
- Interaction effects of antibiotic treatment concurrent with receipt of thimerosal-containing vaccines or immune globulins birth to one month;
- Interaction effects of antibiotic treatment concurrent with receipt of thimerosal-containing vaccines or immune globulins birth to seven months.

Across the models for the 42 outcome measures we found small numbers of statistically significant effects that were roughly balanced between findings where increased exposure was associated with better outcomes, and findings where increased exposure was associated with worse outcomes. For example, in the model used to estimate main effects on the combined group of males and females, higher prenatal exposure was associated with better scores on one outcome measure, and worse scores on another. Cumulative exposure birth to one month was associated with a better outcome on one measure, and a worse outcome for another. Cumulative exposure birth to seven months was associated with better outcomes for two measures. This pattern of results is consistent with what would be expected to occur by chance if exposure had no relationship to outcomes. Using a $p<0.05$ criterion, the expected number of false rejections of the null hypothesis for 42 tests for a single exposure measure (e.g., birth to seven months) is obtained as the product of 0.05 and 42, which is equal to three. The three false rejections of the null hypothesis are expected to be roughly equally distributed between positive and negative associations.

The pattern of finding small numbers of beneficial effects, approximately equally balanced with findings of harmful effects was replicated over all sets of analyses. This type of pattern was found for prenatal, neonatal (birth to 1 month) and birth to 7 months exposure effects for the full sample, for boys, for girls, for interaction effects of prenatal with birth to 7 months exposures, and for interaction effects of antibiotic treatment concurrent with neonatal and birth to 7 months receipt of thimerosal-containing vaccines

or immune globulins. For example, the evaluation of three exposure measures (prenatal, neonatal, birth to 7 months) across the 42 outcome measures, for each of the two sexes required 152 hypothesis tests. Among those tests, 13 were significant at the $p<0.05$ level. The associations were in the direction of increased exposure being associated with better outcomes for seven of the significant tests. The remaining five were in the direction worse outcomes. Under a null hypothesis of no association between exposure and outcomes, the expected number of false rejections of the null hypothesis for 152 tests at the $p<0.05$ level is 13.

Results of two large studies conducted in Great Britain indicated mixes of beneficial and harmful associations between exposure to ethylmercury from vaccines and outcomes similar to those measured in the current study (Heron et al., 2004; Andrews et. al, 2004). Results from the current study showing significant associations between exposures in birth to 7 months and assessor rated motor and phonic tics in boys appear to support two sets of findings from previous studies. The study by Verstraeten et al (2003) found a significant association between exposure and tics at one of three HMOs. And Andrews et al. (2004) found a significant harmful association between exposure and tics in a special sub-analysis. However, Heron et al. (2003) reported a beneficial association between exposure and tics. And among the findings of the current study was a beneficial association between parent reported motor tics and neonatal exposure for girls.

The beneficial associations between exposures and outcomes in the fine motor domain found in the current study coincide with a finding reported by Heron et al. (2003) of a beneficial association between exposure and fine motor skills. However, these findings do not align with the estimated harmful effects of methylmercury exposure from fish consumption on performance on the finger tapping test, as reported by Grandjean et. al. (1997).

The results of models used to test interaction effects between prenatal and postnatal exposure did not support the hypothesis that prenatal exposure would exacerbate the effects of postnatal exposure. Nor did the results of this study support the hypothesis that antibiotic treatment would worsen the effects of postnatal exposure.

We conclude that we did not find clear and convincing evidence of harm. While studies of the sort conducted here cannot disprove the null hypothesis, we consider the pattern of positive and negative associations to be consistent with what we would expect to occur by chance if exposure had no relationship to outcomes. We note, however, that the previously stated caution regarding the threat of selection bias should not be ignored. We urge the reader to consider the results of this study as one piece of evidence in the context of a growing literature on the effects of exposure to ethylmercury.

2. Document Overview

The current document is intended to present both study results and the technical details of study design, sampling, data sources, variable construction, and methods of analysis. This document allows for a more complete presentation of details than was possible within the space constraints on the presentation of the same study published by Thompson et. al. (in press, 2007).

Section 3 presents the historical factors that motivated the study, some background on mercury exposure and its effects on neurological development, the history and use of thimerosal in vaccines, a brief review of the literature on thimerosal and neurodevelopmental outcomes, an introduction to the Centers for Disease Control's research program on thimerosal and vaccines, and the study's motivating research questions. Sections 4, 5, and 6 describe the study's design, sample, and data sources.

Section 7 presents detail on the construction of outcome measures, exposure measures, and covariates. This section also includes an explanation of imputations of missing values on covariates. Section 8 describes the analysis approach. Section 9 presents results. Included in Section 9 are descriptive statistics that describe the characteristics of the study participants and their amounts of exposure to ethylmercury from thimerosal-containing vaccines and immune globulins. The latter part of Section 9 presents summaries of the results of models used to estimate the size and statistical significance of associations between neurodevelopmental outcomes and exposure to ethylmercury from thimerosal-containing vaccines and immune globulins.

3. Background and Research Questions

3.1. Statement of the Problem

During the 1990s the nation's childhood immunization rates increased dramatically. While the overall immunization rate for preschool children was approximately 55 percent in 1992, it rose to 79 percent in 2000. Over approximately the same time period, the recommended number of vaccines to be received by a child during the age range from birth through seven months more than doubled. In 1988, a child immunized according to the recommended schedule[1] would have received three DTP vaccines and two polio shots during his/her first seven months of life. By 1999, a child immunized according to the recommended schedule would have received as many as three hepatitis-b vaccines, three DTaP vaccines, three Hib vaccines, and three polio shots during his/her first seven months. Over the same approximate time frame the rates of diagnoses of a range of neurodevelopmental diseases such as autism and attention hyperactivity deficit disorder (ADHD) increased dramatically (Mandell et. al., 2005; Newschaffer et. al, 2006).

Until the phase-out of thimerosal-containing childhood vaccines that began in 1999, many of the regularly administered infant vaccines contained mercury. Thimerosal, which had been used as a preservative in vaccines since the 1930s, is 49.6% mercury by weight and is metablolized into ethylmercury and thiosalicylate.

In 1999, the U.S. Food and Drug Administration (FDA) estimated that adherence to the schedule of immunizations recommended by the Advisory Committee on Immunization Practices (ACIP) could result in ethylmercury exposure that exceeded the Environmental Protection Agency's (EPA) limits for methylmercury exposure. At the time, there was little known about similarities or difference in the metabolism and excretion of these two forms of mercury, but the chemical similarities of the two, combined with the known toxic effects of exposure to methylmercury, was cause for alarm.

Consequently, the U.S. Public Health Service and the American Academy of Pediatrics urged vaccine manufacturers to removed thimerosal from all infant vaccines as soon as possible, and recommended that studies be carried out to assess the risks associated with exposure to mercury from thimerosal-containing vaccines.

3.2. Background on Mercury

Mercury is an element that cycles through three different chemical forms in the environment: methylmercury, ethylmercury, and phenylmercury. Research has confirmed that determination of the toxicity of mercury is complicated and dependent on the form of mercury, route of entry, dose, and age at exposure (AAP, 1999). Humans are exposed to mercury in its different forms from various sources. Modern industrial

[1] The vaccine schedule recommended and approved by the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP).

processes, especially fossil fuel combustion and waste incineration, are responsible for a recent dramatic increase in environmental levels of methylmercury. The major source of non-occupational methylmercury exposure is dietary intake, with fish and seafood as the main sources because of their propensity to bioaccumulate mercury up the food chain. Vaccinations are the major source of exposure to ethylmercury, because the Thimerosal used as a preservative contains 49.6 percent mercury by weight and is metabolized to ethylmercury and thiosalicylate (AAP, 1999; Pless and Risher, 2000).

The major impact of organic mercury compounds is on the central nervous system, although the kidneys and the immune system also may be affected. Furthermore, organic mercury easily crosses placenta and blood-brain barriers (AAP, 1999). Although the CDC and others have recently made strides in understanding the effects of the ethylmercury in Thimerosal-containing vaccines, the exact nature of toxicity and neurodevelopmental effects from exposure are essentially unknown. At doses considerably higher than what the children would be exposed to from a normal schedule of vaccines, ethylmercury has been reported to cause neurotoxicity, but the effects of exposure to low concentrations have not been established (Ball et al., 2001).

Much of the concern about the potential hazards of ethylmercury comes from research on the effects of mercury in the form of methylmercury. Below we summarize the research on methylmercury neurotoxicity and present the argument for its relevance to concerns about possible ethylmercury toxicity from Thimerosal exposure.

3.3. Research on Neurotoxicity of Methylmercury

Research on the adverse effects of human mercury exposure dates to the 1950s, when the consumption of fish contaminated by industrial waste in the Minamata Bay region of Japan was linked to an epidemic of severe neurological disease (Harada, 1995). A similar epidemic occurred in Iraq in the 1970s from consumption of mercury-containing fungicide in seed grain (Bakir et al., 1973; Marsh et al., 1980). In both these outbreaks mercury poisoning was documented in all age groups, but infants seemed particularly vulnerable, and maternal methylmercury exposure was associated with nervous system abnormalities, such as mental retardation and impaired motor function among children exposed in utero. In the Minamata epidemic, some infants with severe brain damage were born to exposed mothers who were themselves barely affected. Similar effects on infants were seen in the Iraqi outbreak, which also raised questions about more subtle, delayed effects of prenatal exposure. These epidemics provided strong evidence linking exposure to high levels of methylmercury with severe neurological damage, and also led to the confirmation of mercury as a neurotoxicant and to the establishment of early exposure guidelines.

Concern about the potential health threat from methylmercury grew in the early 1970s when elevated concentrations were found in fish from the Great Lakes. Inorganic mercury released into large bodies of water is converted to methylmercury by microorganisms and bioaccumulated up the aquatic food chain (Davidson et al., 1998; Mahaffey, 1999). Accumulation of mercury in fish can result in increased human

exposures to this metal, particularly in populations whose diets include a high intake of marine food (Turner et al., 1980).

Recently, increased attention has focused on what levels of exposure to methylmercury can be considered safe. Agencies such as the World Health Organization (WHO), the U.S. Environmental Protection Agency (EPA), the U.S. Agency for Toxic Substances and Disease Registry, and the U.S. Food and Drug Administration (FDA) provide recommendations for safe exposure to methylmercury in the diet; suggested "safe" levels range from 0.7 μg/kg bodyweight/week (EPA) to 3.3 μg/kg bodyweight/week (WHO) (Clements et al., 2000). Most recommendations for methylmercury exposure limits are based on data from the Iraqi epidemic (Bakir et al., 1973; Marsh et al., 1980), but because the exposures in Iraq were about six months in duration and at high concentrations, questions remain about generalizing the effects of this exposure period and concentration level (Mahaffey, 1999). Recently, however, epidemiological studies of lower levels of methylmercury exposure have begun to emerge, heightening concern over potential effects of chronic, low level exposure to methylmercury, particularly for children exposed prenatally from maternal fish consumption.

3.3.1. Neurological Effects of Children's Dietary Exposure to Methylmercury

In 1998, conflicting findings from two seminal studies on the effects of children's dietary exposure to methylmercury prompted the White House Office on Science and Technology Policy (OSTP) to convene a multi-agency scientific review of risks associated with chronic, low levels of methylmercury exposure (National Institute of Environmental Health Sciences, 1998). Both of these studies, located in vastly different geographic areas, one in the Seychelle Islands in the Indian Ocean (Davidson et al., 1998) and the other in the Faroe Islands in the North Atlantic (Grandjean et al., 1997), are longitudinal examinations of children's neuropsychological functioning after prenatal exposure to methylmercury, in which mothers were enrolled in the studies during pregnancy and their child's development was followed into elementary school.

Both the Faroese and Seychellois consume a steady fish diet; the Faroese also consume intermittent meals of pilot whale muscle. Despite comparable mercury levels from maternal hair samples in the two populations—a geometric mean of 4.3 ppm in the Faroe Islands (Grandjean, et al., 1997) and an arithmetic mean of 6.8 ppm in the Seychelles (Davidson, et al., 1998)—investigators came to opposite conclusions about the effects of mercury exposure on children's intellectual functioning. In the Seychelle Islands, a preliminary pilot study revealed effects of prenatal methylmercury exposure on several neurobehavioral assessments, but the researchers discounted these results when the exclusion of four "outlier" cases from the analysis dropped the effects below statistical significance and because the pilot failed to include potential socioenvironenmental confounding variables (Myers et al., 1995). In the subsequent main study, researchers found no association between 5.5-year-olds' performance on global assessments of intellectual functioning and mercury exposure measured in maternal hair samples (Davidson et al., 1998). In contrast, Faroe Islands investigators reported that each

doubling in prenatal mercury exposure corresponded to a delay of one to two months in mental development at age seven (Grandjean et al., 1997).

In an attempt to account for these divergent findings, the OSTP panel identified five major differences between the studies (Jacobson, 2001). First, the determination of mercury exposure in the Faroe Islands study included measurement of the concentration of methylmercury in umbilical cord blood, which primarily indicates exposure occurring during the last trimester, a time of relatively rapid neuronal development. In the Seychelles Islands study, the measure of mercury exposure was limited to maternal hair samples, which reflect exposure over the entire pregnancy. Second, children in the Seychelles Islands study were assessed at 5.5 years, an age during which rapid developmental change and substantial individual differences in maturation may mask neurodevelopmental delays, whereas children in the Faroe Islands study were assessed at age 7, a time of relative developmental stability (Jacobson and Jacobson, 1991). Third, the assessments used in the Faroe Islands study were targeted at specific domains of neuropsychological functioning, including measures sensitive to particular aspects of function in language, memory, and attention, in contrast to more global measures of cognitive functioning used in the Seychelles study. Thus, the measures and timing of assessments in the Faroes study may have been better suited to detect an association between exposure and neurodevelopmental delays. In addition to these methodological differences, panelists identified two potentially important environmental differences. First, the Seychellois' steady diet of fish the Faroese diet includes intermittent consumption of pilot whale meat, a source of methylmercury concentrations 10-20 times stronger than those in fish (Grandjean, et al., 1992). Second, because environmental contaminants tend to be transported northward along prevailing currents, the North Atlantic region in which the Faroe Islands are located is subjected to much stronger concentrations of polychlorinated biphenyls (PCBs) than the Seychelles Islands in the Indian Ocean. Some panelists suggested that prenatal methylmercury exposure may affect neurodevelopment only in the presence of significant PCB exposure (Jacobson, 2001).

The OSTP panel concluded that uncertainty remained over low levels of methylmercury exposure from fish (NIEHS, 1998). Subsequently, however, a National Academy of Sciences panel conducted further examination of these same two studies in conjunction with other data not considered by the OSTP panel. The NAS panel's findings cast doubt on the explanations offered to account for differences in the Faroese and Seychellois findings.

Specifically, the NAS panel evaluated the findings in light of a New Zealand study conducted in the 1980s but published without formal peer review (Kjellstrom et al., 1989). Though similar in methodology to the Seychelles Island study, the New Zealand investigators did find effects of methylmercury. As in the Seychelles study, the New Zealand study: used maternal hair samples to measure methylmercury exposure; included a global assessment of intelligence; and focused on a population likely exposed to very low levels of PCBs. Moreover, the New Zealand study tested children close in age (i.e., six-year-olds) to the 5.5-year-olds in the Seychelles. Finally, the diet of the New

Zealanders was similar to that of the Seychellois, in that neither population consumed whale meat; thus, the episodic peak doses of high levels of methylmercury among the Faroese could not account for the differences in the conclusions of the two islands studies. In light of these findings, arguments that research design differences between the Faroese and Seychellois studies could account for their conflicting conclusions were deemed no longer persuasive (National Research Council, 2000). Further analysis by the NAS panel suggested that the Seychelles study may have lacked sufficient power to detect the relatively small effect sizes computed for the Faroe Islands data (NRC, 2000; Jacobson, 2001).

Because the data from all three studies more likely represent the typical exposure scenario of North American populations than did the Iraqi experience, the NAS panel recommended that the EPA compute a new reference dose for methylmercury. In light of their evaluation of the Faroese, Seychellois and New Zealand studies and the burden of preventing potential risks to public health, the NAS panel argued that the positive findings from the Faroe Islands data be accorded more weight than the lack of findings among the Seychellois cohort. Nevertheless, the NAS panel could not fully account for the lack of findings in the Seychellois studies.

3.3.2. Mercury Exposure May Present Greater Risk for Infants

Despite unresolved differences in the findings of the Faroese and Seychellois studies, scientific review indicates general concern over the health effects of human exposure to even low levels of mercury, particularly for infants. The developing fetus and young children may be disproportionately affected by mercury exposure because many aspects of development, particularly brain maturation, can be disturbed by the presence of mercury (Mahaffey, 1999). Because newborns may have decreased ability to both oxidize and eliminate mercury (Goldman et al., 2001), the resulting higher concentrations of unoxidized mercury for longer durations than would typically be found in adults could lead to toxic levels of accumulation. In addition, the primary way that the body gets rid of mercury is through bile, which infants do not produce (AAP, 1999). Also, the long half-life of methylmercury (average 50 days) results in accumulation that could be harmful to the developing fetal brain, which is much more susceptible to organomercurial compounds than is the adult brain (Choi, 1989).

3.4. Uses of Thimerosal in Vaccines

Thimerosal is necessary for use as a preservative only when the vaccine is packaged in a multi-dose vial. In this circumstance, the thimerosal acts as a preservative to protect the remaining doses of the vaccine from bacterial and fungal contamination after a single dose is administered. Although in the United States multi-dose vials are currently not being used for vaccines administered as part of the recommended childhood immunization schedule, they remain the only option in many parts of the developing world, as they are less expensive and require less storage space (Ball et al., 2001).

In the late 1990s, childhood vaccines that contained thimerosal included hepatititis-b (HepB) vaccines , diphtheria-pertussis-tetanus (DPT) vaccines, some Haemophilus influenzae type b (HiB) vaccines, and the influenza vaccine. An additional potential source of mercury exposure was from receipt of hepatitis B immune globulins. Polio and measles-mumps-rubella vaccines did not contain thimerosal.

In addition to the postnatal sources of thimerosal, in utero exposure was possible via administration of thimerosal-containing preparations administered to mothers during pregnancy. These included the influenza, tetanus, hepatitis B, and diphtheria-tetatnus vaccines, and anti-Rh immunoglobulins, which is used to suppress Rh-sensitization in Rh-negative mothers who give birth to Rh-positive babies.

In addition to its use as a preservative, thimerosal is used as an inactivating agent in the manufacture of certain vaccines, and as a bacteriostatic agent during the production process of other vaccines (Ball et al., 2001). Its use in manufacturing and production processes, however, contributes little to the final concentration of ethylmercury in a single vaccine. In the 1990s, receipt of a hepatitis B vaccine would result in exposure to 12.5 micrograms of ethylmercury from the thimerosal used as a preservative. Most DTP and Hib vaccines in use at that time would have resulted in exposure to 25 micrograms of ethylmercury from the thimerosal used as a preservative, for each receipt. In contrast, thimerosal's use in manufacturing and production results in, at most, exposure to 0.25 to 0.75 micrograms of ethylmercury per vaccine receipt (Ball et al., 2001)[2].

3.5. Recommendation to Remove Thimerosal from Infant Vaccines

In July of 1999 the U.S. Public Health Service and the American Academy of Pediatrics issued a joint statement which established the goal of removing thimerosal as soon as possible from vaccines customarily recommended for infants (AAP, 1999). Until sufficient supplies of thimerosal-free vaccines were available, recommendations were made to postpone the first hepatitis B (HepB) vaccine dose until two to six months of age for infants born to hepatitis B-negative women, to avoid exposing newborn children to ethylmercury at a time when they were especially vulnerable to neurotoxicity because of their small body mass and their inability to excrete the ethylmercury effectively. Pediatricians were further advised that the use of thimerosal-containing vaccines was preferred to withholding vaccinations if no alternative was available

At the time of the recommendation, little was known about the toxicity of ethylmercury and a review by Ball et al., (2001) revealed no evidence of harm caused by the doses of thimerosal found in vaccines, except for local hypersensitivity reactions. That is, when vaccines containing thimerosal had been administered in recommended doses, hypersensitivity had been noted, but no other harmful effects had been reported (CDC, 2000). The case against ethylmercury was made primarily on the basis of the data on the

[2] Ball et. al (2001) report that these processes result in a maximum of 2-3 micrograms of thimerosal / mL. Thimerosal is 49.6% mercury by weight. Multiplication of of relevant terms yields an estimate of 0.5 – 0.75 micrograms of mercury per 0.5 mL dose.

toxicity of methylmercury and clinical similarities between cases of ethyl- and methylmercury poisoning.

Two ethylmercury epidemics in Iraq in the 1960s were remarkably similar to the methylmercury epidemics that occurred there in the 1970s: victims had consumed grain, or animals fed grain, that had been improperly treated with an ethylmercury-containing fungicide (Damluji, 1962; Jalili and Abbasi, 1961). The range of symptoms reported included difficulty walking, ataxia, other motor function impairment, speech disorders, and visual field constriction. In addition to such dietary exposure, there are also reports of neurologic symptoms in patients who received large overdoses of ethylmercury from medicinal preparations (e.g., Axton, 1972; Fagan et al., 1977; Lowell et al., 1996). For example, a liver transplant patient given high doses of hepatitis-B immunoglobulins in preparations containing thimerosal developed speech articulation difficulties, general slowing of motor movements, and an inability to walk; chelation therapy eliminated these symptoms within four to five weeks (Lowell et al., 1996). Interestingly, hair samples indicated that he had had prior environmental exposure to mercury, though from an undetermined source.

Although ethylmercury, in sufficiently high doses, has neurotoxic properties similar to those of methylmercury, the relative toxicities of ethylmercury and methylmercury had not been well established (Ball et al., 2001). At the time of the recommendation for removal of thimerosal, the effect of intermittent intramuscular doses of thimerosal-containing vaccines on neurodevelopmental outcomes had not been studied. One study did measure the effect of a single dose of a thimerosal-containing HepB vaccination, administered within three days of birth, on infants' blood-mercury levels. With one 0.5 mL dose of the vaccine (approximately 12.5 μg of mercury), the mean mercury blood level increased from . 54 to 7.36 μg/L in 15 preterm infants and .04 to 2.24 μg/L in five term infants. These were statistically significant increases (Stajich et al., 2000). Therefore, a birth dose of the hepatitis B vaccine may measurably increase infant blood mercury levels.

Calculations of the maximum potential exposure to ethylmercury from recommended childhood immunization schedules in effect in the 1990s suggest that infants could receive total doses of ethylmercury in excess of various agencies' exposure limits for methylmercury during the first six months of life (Ball et al., 2001). The exact dosage of thimerosal received depended on the vaccine schedule followed by the child and the manufacturer of the vaccine, but a worst-case scenario would be an infant who received a series of vaccinations resulting in a maximum exposure to ethylmercury by age six months that could reach approximately 187.5 μg. With limits for safe methylmercury exposure between 34 and 159 μg, this suggested that some infants may have received doses of mercury from vaccines that may have been of concern (WHO, 2000). An additional issue was that infants may not eliminate mercury as efficiently as older children or adults (Goldman et al., 2001).

3.6. Research on Neurotoxicity of Ethylmercury/Thimerosal

Subsequent to the recommendation to remove thimerosal from childhood vaccines several studies have been published that focus on the relationships between exposure to ethylmercury from thimerosal-containing vaccines and neurodevelopmental outcomes of children. These include studies by Verstraeten et al. (2003), Hviid et. al. (2003), Geier and Geier (2003a, 2003c, 2003c, 2004, 2005, 2006a, 2006b), Heron et. al. (2004), Andrews et. al. (2004), and Fombonne et al. (2006).

The study by Verstraeten et al. (2003) calculated measures of exposure and outcomes using computerized records of three large HMOs. These records were developed and maintained as part of the Vaccine Safety Datalink (VSD) system, and as part of administrative record keeping systems. Three measures of exposure were calculated from the computerized records of vaccine receipts. These were cumulative mercury exposure from birth to 1 month, cumulative mercury exposure from birth to 3 months, and cumulative mercury exposure from birth to 7 months. Outcome measures were obtained from ICD-9 codes[3] and were coded as the presence/absence of diagnoses of neurodevelopmental disorders. Outcomes included autism, "other child psychosis", stammering, tics, sleep disorders, eating disorders, emotional disturbances, ADD, developmental language delay, developmental speech delay, speech or language delay, and coordination disorder. Results were reported separately for each of the three HMOs.

The study reported no significant associations between outcomes and 1-month cumulative exposure for any of the three HMOs. Significant findings were reported for associations between 3-month cumulative exposure and tics at one HMO, and 3-month exposure and language delay at a second HMO, and between 7-month cumulative exposure and language delay at the same HMO.

The study had several important design weaknesses. First, it relied on physician diagnosis of childhood neurodevelopmental delays and other developmental outcomes, rather than a standardized assessment of children's developmental status. Physician diagnosis is likely to introduce unreliability in the outcome measures, since different physicians may be using different criteria for classifying children as developmentally delayed or as demonstrating behavioral problems such as ADHD. Second, using physician diagnosis introduces the possibility of bias in the measurement of child outcomes, since children from families that are more attentive to seeking health care may be both more likely to receive a diagnosis and more likely to have received all of his/her vaccinations on time, thus potentially having higher ethylmercury exposure. Third, the study did not have family demographic information and therefore the analyses could not control for factors known to be associated with the outcomes.

The study by Hviid et al. (2003) used computerized records corresponding to all children born in Denmark over the period January 1, 1990 to December 31, 1996, to estimate the relative risk of autism corresponding to cumulative ethylmercury exposure amounts of 0, 25, 75, and 125 micrograms. No significant associations were reported.

[3] ICD-9 = International Classification of Diseases, Nineth Revision, Clinical Modification.

Each of the Geier and Geier (2003a, 2003c, 2003c, 2004, 2005, 2006a, 2006b) studies reported finding associations between thimerosal-containing vaccines and neurodevelopmental disorders. However, the Institute of Medicine (IOM) (2004), characterized the first four of those studies (2003a, 2003c, 2003c, 2004) as having serious methodological limitations that render the results uninterpretable. Parker et. al, (2004) also identifies multiple methodological concerns with the same studies. Like the earlier studies, the latter three papers (2005, 2006a, 2006b) report results of analyses of the Vaccine Adverse Events Reporting System (VAERS) database. Detailed descriptions of potential biases and pitfalls that could arise from attempting to use the VAERS data to make causal inferences are provided in IOM (2004) and Parker et. al (2004).

In addition to the results from analysis of VAERS data, the Geier and Geier (2005) paper reports results from analyses of VSD data. Although the authors of the Geier and Geier (2005) paper claim to have analyzed the VSD data as independent researchers, major sections the text and several tables match almost identically to text and tables included in a preliminary draft of the Verstraeten et. al. paper, described above[4].

The results reported by Heron et al (2004) were based on a study of over 13,000 children in the United Kingdom. Exposure data came from the Bristol-based Child Health Surveillance Database. Outcome measures were created from maternal responses to the Strengths and Difficulties Questionnaire and the Child Behavior Checklist (behavior ratings), the Revised Denver Scale (fine motor development) and from other items in the maternal questionnaire (speech problems, tics, and special needs). Results of 69 hypothesis tests (23 outcomes times 3 exposure measures) from models that controlled for birth weight, gestation, maternal education, and other demographic characteristics of the child and family indicated nine significant associations between exposures and outcomes. One was in the direction of increased exposure being related to harm, the remaining 8 were in the direction of benefit. Poor prosocial behavior at 47 months of age was associated with higher 3-month exposure. Outcomes with associations in the direction of benefit were conduct problems, fine motor skills at 30 months of age, tics at 91 months of age, and two measures that are each indicators that the child has special needs. Several of these 5 beneficial outcomes had significant associations with two exposure measures, totaling 8 significant hypothesis tests.

The results reported by Andrews et al. (2004) were based on data obtained from over 103 thousand children. Exposure and outcome data were extracted from computerized medical records. Outcome measures were created from ICD-9 codes. Confounder variables used in their statistical models included gender, year of birth, and when significant, month of birth. They reported beneficial associations between increased exposure and general developmental disorders, ADD, speech or language delay, and

[4] Early pre-publication write-ups of the Verstraeten et. al. analyses obtained via the Freedom of Information act were posted on a web site and, at the time of this writing, are currently available on the web. See Verstraeten et. al. (2000) for details. For criticism regarding the differences in findings between preliminary and final analyses conducted by Verstraeten et. al. see Redwood (2004). For a response to criticism, see Verstraeten (2004).

unspecified developmental delay. In a special sub-analysis that excluded children who had not received all three recommended DTP vaccinations by one year of age, a significant harmful association between increased exposure and tics was found. In the full data set, the estimates for tics were in the harmful direction, but not statistically significant.

Fombonne et al. (2006) estimated the prevalence of pervasive developmental disorder (PDD) in cohorts of children in Montreal Canada over a span of time that included the removal of thimerosal from childhood vaccines. They reported a statistically significant linear trend in the prevalence of PDD during the study period. They also reported that the prevalence of PDD in thimerosal-free birth cohorts was significantly higher than that in thimerosal-exposed cohorts. They concluded that thimerosal exposure was unrelated to the increasing trend in PDD prevalence in Montreal Canada.

3.6.1.1. The CDC Research Program

To study the potential health risks of thimerosal in vaccines, the CDC has utilized data from a vaccine safety monitoring project (the VSD) and has mounted a program of research that includes a series of studies.

The CDC established the VSD Project in 1990 to improve the capability to study side effects of vaccines through large-linked databases of computerized vaccination and medical records. This project involves partnerships with several large HMOs to continually monitor vaccine safety. The database includes information on more than six million people. All vaccines administered within the study population are recorded, as well as data on vaccine type, date of vaccination, concurrent vaccinations, manufacturer, lot number, and injection site. Records are monitored for potential adverse events resulting from immunization.

The first in the CDC's series of studies on health effects of exposure to thimerosal was the *screening study* by Verstraeten et al. (2003), described previously. The intent of this study was to determine if there were any adverse associations that could be subsequently investigated using more rigorous study designs.

The next three studies in the CDC's series of investigations were:

- *The Infant Environmental Exposures and Neurodevelopmental Outcomes at Ages 7-10 Years* – This study is the focus of this report. This study was designed to follow-up on the conflicting results from the screening study, as well as the results Sechelles and Faroe Islands studies. To overcome some of the methodological limitations of the screening study, the current study conducted in-person assessments of children using a standardized battery of neuropsychological assessments, sampled children based on vaccine exposure without regard health care utilization or neurodevelopmental diagnosis, and included extensive additional data on potential confounding factors.

- *The Italian Trial on Acellular Pertussis Vaccines* – This study compares neuropsychological outcomes of children at ages 10-12 years that were randomly assigned to receive either of two forms of diphtheria-tetanus-acellular pertusis vaccine (DTaP) in the first year of life. One of the two forms of DTaP included thimerosal as a preservative, the other included 2-phenoxyethanol as a preservative. Children that received the thimerosal-containing DTaPs had cumulative exposure to 137.5 micrograms of ethylmercury during the age range spanning birth to twelve months, from all vaccines including hepatitis-b receipts, while children receiving the other form of DTaP had total cumulative exposure of 62.5 micrograms during the same age range. The study is currently in progress.

- *The Autism Case-Control Study* – This study is using a case-control design to investigate whether there are associations between exposure to mercury from thimerosal-containing vaccines and immune globulins, and autistic disorder and autism spectrum disorder. At the time of this writing, data collection was underway for this study.

3.7. Research Questions for the Current Study

The primary research questions that motivated the design and guided the analyses were as follows:

1) Is there an association between neuropsychological outcomes and cumulative exposure to mercury from thimerosal-containing vaccines and immune globulins received during the age range spanning birth to seven months?

2) Is there an association between neuropsychological outcomes and cumulative exposure to mercury from thimerosal-containing vaccines and immune globulins received during the age range spanning birth to one month?

3) Is there an association between neuropsychological outcomes and prenatal exposure to mercury from thimerosal-containing vaccines and immune globulins received by the mother during her pregnancy with the focus child?

Secondary research questions motivated additional analyses. These were:

- Do exposure effects vary by the sex of the child?
- Does prenatal exposure to mercury modify the effects of postnatal exposure to mercury from thimerosal-containing vaccines and immune globulins?
- Does receipt of antibiotics, concurrent with receipt of thimerosal-containing vaccines or immune globulins, modify the exposure effects?

4. Study Design

The current study utilized a retrospective cohort design[5] (Kleinbaum, Kupper, & Morgenstern, 1982) wherein historical (administrative) data were used to select a cohort of children with a wide range of cumulative exposure to ethylmercury from thimerosal during the age range spanning birth to seven months. This cohort of children was "followed" into the present, when the children were in the age range of 7-10 years, at which time outcomes were measured using a battery of neurodevelopmental assessments

Inferences regarding the relationships of prental and early childhood exposure to ethylmercury from thimerosal-containing vaccines and immune globulins to neurodevelopmental outcomes were made from results of linear and logistic regression models where outcomes were modeled as functions of the exposure variables, covariates, and residual error.

The choice of which tests to include in the battery of assessments was guided by the results of the Faroe Islands study (Grandjean et al., 1997), the Sechelles Islands study (Davidson et al., 1998), and the CDC screening study (Verstraeten et al., 2003)), and by the recommendations from the External Expert Consultants. Outcomes that were found to have associations with mercury exposure in any of those studies were considered to be important outcomes for the current study. The battery of outcome assessments included measures of speech and language, verbal memory, literacy achievement, fine motor coordination, visual spatial ability, attention / executive functioning, behavior regulation, tics, and general intellectual functioning.

Data on prenatal and early childhood exposure to ethylmercury from thimerosal-containing vaccines and immune globulins were obtained from several sources: Medical record abstractions, computer-automated medical records that are maintained as part the Vaccine Safety Datalink system or as part of HMO administrative records, parent-provided immunization records, and parent interview.

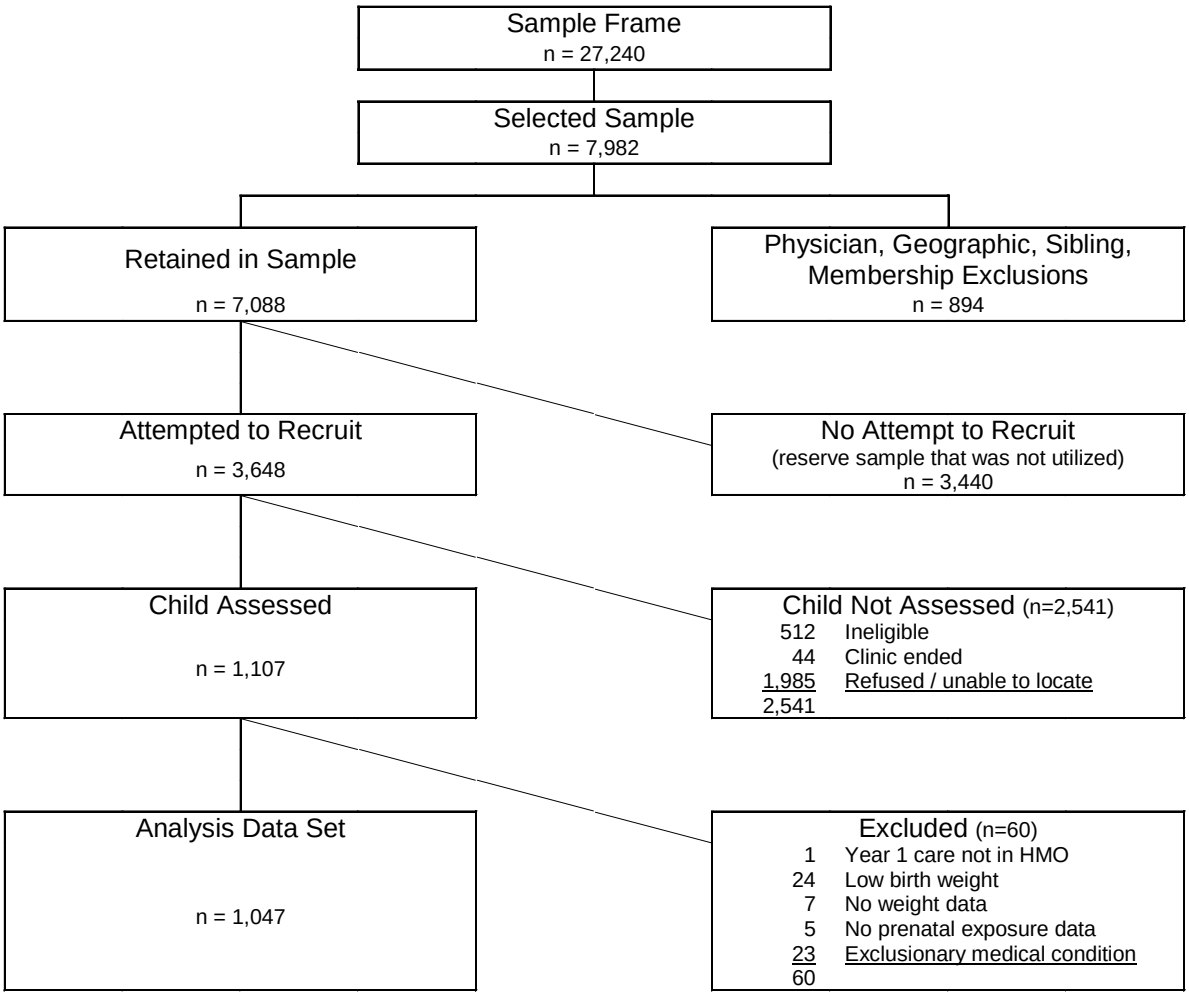
Measures of child and family demographic characteristics, child birth conditions, prental and childhood exposure to neurotoxins, child medical conditions, and measures of maternal diagnoses of speech delay, language delay, stuttering and attention deficit hyperactivity disorder were used as covariates. The data required to construct these measures were obtained from parent interview and from child and maternal medical record abstraction.

[5] Also known as a historical prospective design (Mausner & Bahn, 1985)

5. Sample

The sample of study participants was drawn from a sampling frame created from VSD records from four participating health maintenance organizations (HMOs). Eligibility criteria are described in Section 5.1. The steps from creation of the sampling frame, to sample selection, to recruitment and data collection, to creation of the final analysis sample are depicted in the flow chart in Exhibit 5.1 and are described in subsequent sections. The numbers appear smaller in each successive step as samples and sub-samples were drawn, as new information on eligibility was acquired in several steps that necessitated the omission of ineligible children, and for other reasons such as inability to locate families or families' refusal to participate.

Exhibit 5.1. Data Collection Flow Chart



5.1. Eligibility Criteria

Eligibility criteria are listed in Exhibit 5.2. Children with particular medical conditions were excluded from the study. The list of exclusionary medical conditions was developed by a team of five pediatricians from the CDC and from the HMOs. These conditions had to be present at birth or diagnosed and recorded before the first birthday, and were conditions that were deemed likely to have adverse effects on neurodevelopmental outcomes. Most exclusions due to medical conditions were applied during the creation of the sampling frame, using ICD-9 codes from the VSD database. Other exclusions were applied at the time of the telephone eligibility interview, and a small number of exclusions were applied only after the sample child's medical records had been abstracted. Exclusionary medical conditions are shown Exhibit 5.3. Additionally, children who had ever been diagnosed with lead poisoning, or who had ever had blood lead levels greater than 10 were excluded, as were children with uncorrected hearing loss.

Prior to recruitment, the children's primary care physicians were informed of the names of their patients that were selected to participate in the study, and the physicians had the opportunity to exclude any or all their patients if they so desired.

Exhibit 5.2. Eligibility Criteria

Eligibility Criterion	Comments
Child's birth date between Jan 1, 1993 and Dec 31, 1997	Children born during this period would be 7 to 10 years of age at the time of assessment.
Child is currently a member of HMO.	This criterion increased the likelihood that current contact information would be available for sample members.
Child must be born into HMO system	This criterion increased the likelihood of having complete prenatal and birth records
Child must be a member of HMO for entire first year of life.	This criterion increased the likelihood of having a complete vaccination history and medical records for entire first year of life.
Child must have received all year 1 vaccinations at HMO	This criterion increased the likelihood of having complete vaccination for entire first year of life.
Child must not have received any experimental vaccines that had unknown thimerosal amounts.	If thimerosal amount was unknown, accurate ethylmercury exposure could not be ascertained.
Child must not have any siblings in the sample.	If two or more eligible children from a single family were randomly selected for inclusion in the sample, only one of the children, chose at random, was retained in the sample.
Child and mother must speak English well enough to participate in English language interviews and/or assessments.	Assessment of English language ability was assessed during eligibility and recruitment calls.
Child must be singleton.	Twins, triplets, multiple births were excluded.
Child must live with biological mother at least 4 days per week on average.	Child must live with biological mother to ensure that questions on parent interview about prenatal and early experiences could be answered, and must live with mother at least 4 days per week to ensure that mother is very knowledgeable about child's development.

Exhibit 5.2. Eligibility Criteria

Eligibility Criterion	Comments
Child must not have been taking antidepressant or anticonvulsant medication or have been taking Clonopin (a type of antihypertension medication).	
Child must live within 50 miles of the clinic site where assessments were administered.	
Child must not have had any of the exclusionary medical conditions listed in Exhibit 5.3.	The exclusionary conditions were medical conditions diagnosed within the first year of life that are known or expected to be associated with poor scores on the outcome measures.
Children who had ever been diagnosed with lead poisoning, or who had ever had blood lead levels greater than 10 were excluded.	
Children with uncorrected hearing loss were excluded.	

Exhibit 5.3. Exclusionary Medical Conditions

ICD-9 Code	Condition
	Low birth weight (<2500 grams)
0478	VIRAL MENINGITIS NEC
0479	VIRAL MENINGITIS NOS
0490	LYMPHOCYTIC CHORIOMENING
0498	VIRAL ENCEPHALITIS NEC
0499	VIRAL ENCEPHALITIS NOS
24200	TOX DIF GOITER NO CRISIS
243	CONGENITAL HYPOTHYROIDSM
244	ACQUIRED HYPOTHYROIDISM*
2440	POSTSURGICAL HYPOTHYROID
2443	IATROGEN HYPOTHYROID NEC
2449	HYPOTHYROIDISM NOS
245	THYROIDITIS*
2452	CHR LYMPHOCYT THYROIDIT
2459	THYROIDITIS NOS
2461	DYSHORMONOGENIC GOITER
2462	CYST OF THYROID
2468	DISORDERS OF THYROID NEC
2469	DISORDER OF THYROID NOS
3200	HEMOPHILUS MENINGITIS
3201	PNEUMOCOCCAL MENINGITIS
3202	STREPTOCOCCAL MENINGITIS
3203	STAPHYLOCOCC MENINGITIS
32081	ANAEROBIC MENINGITIS

Exhibit 5.3. Exclusionary Medical Conditions

ICD-9 Code	Condition
32082	MNINGTS GRAM-NEG BCT NEC
3209	BACTERIAL MENINGITIS NOS
3222	CHRONIC MENINGITIS
3229	MENINGITIS NOS
3231	RICKETTSIAL ENCEPHALITIS
3234	OTH ENCEPHALIT D/T INFEC
3236	POSTINFECT ENCEPHALITIS
3239	ENCEPHALITIS NOS
3240	INTRACRANIAL ABSCESS
325	PHLEBITIS INTRCRAN SINUS
326	LATE EFF CNS ABSCESS
330	CEREBRAL DEGEN IN CHILD*
3300	LEUKODYSTROPHY
3301	CEREBRAL LIPIDOSES
3308	CEREB DEGEN IN CHILD NEC
3309	CEREB DEGEN IN CHILD NOS
36900	BOTH EYES BLIND-WHO DEF
36923	ONE EYE-MODERATE/OTH-NOS
36960	BLINDNESS, ONE EYE
3699	VISUAL LOSS NOS
3897	DEAF MUTISM NEC
7400	ANENCEPHALUS
7401	CRANIORACHISCHISIS
7410	SPINA BIF W HYDROCEPHAL*
74100	SPIN BIF W HYDROCEPH NOS
74103	SPIN BIF W HYDRCEPH-LUMB
7420	ENCEPHALOCELE
7421	MICROCEPHALUS
7422	REDUCTION DEFORM, BRAIN
7423	CONGENITAL HYDROCEPHALUS
7424	BRAIN ANOMALY NEC
74300	CLINIC ANOPHTHALMOS NOS
74310	MICROPHTHALMOS NOS
74312	MICROPHTH W OTH EYE ANOM
7433	CONG CATARACT/LENS ANOM*
74330	CONGENITAL CATARACT NOS
74335	CONGENITAL APHAKIA
74339	CONG CATAR/LENS ANOM NEC
74343	CONG CORNEAL OPACIT NEC
7467	HYPOPLAS LEFT HEART SYND

Exhibit 5.3. Exclusionary Medical Conditions

ICD-9 Code	Condition
74682	COR TRIATRIATUM
747	OTH CONG CIRC SYST ANOM*
74869	LUNG ANOMALY NEC
749	CLEFT PALATE & CLEFT LIP*
7490	CLEFT PALATE*
74900	CLEFT PALATE NOS
74901	UNILAT CLEFT PALATE-COMP
74902	UNILAT CLEFT PALATE-INC
74903	BILAT CLEFT PALATE-COMPL
74904	BILAT CLEFT PALATE-INC
7491	CLEFT LIP*
74910	CLEFT LIP NOS
74911	UNILAT CLEFT LIP-COMPL
74912	UNILAT CLEFT LIP-IMCOMPL
74914	BILAT CLEFT LIP-INCOMPL
7492	CLEFT PALATE W CLEFT LIP*
74920	CLEFT PALATE & LIP NOS
74921	UNIL CLEFT PALAT/LIP-COM
74922	UNIL CLEFT PALAT/LIP-INC
74923	BILAT CLFT PALAT/LIP-COM
74924	BILAT CLFT PALAT/LIP-INC
74925	CLEFT PALATE & LIP NEC
75010	TONGUE ANOMALY NOS
75012	CONG ADHESIONS OF TONGUE
75015	CONG MACROGLOSSIA
75019	TONGUE ANOMALY NEC
75026	MOUTH ANOMALY NEC
75029	PHARYNGEAL ANOMALY NEC
7507	GASTRIC ANOMALY NEC
7560	ANOMAL SKULL/FACE BONES
75616	KLIPPEL-FEIL SYNDROME
758	CHROMOSOMAL ANOMALIES*
7580	DOWN'S SYNDROME
7581	PATAU'S SYNDROME
7582	EDWARDS' SYNDROME
7583	AUTOSOMAL DELETION SYND
7584	BALANCE AUTOSOM TRANSLOC
7585	AUTOSOMAL ANOMALIES NEC
7586	GONADAL DYSGENESIS
7587	KLINEFELTER'S SYNDROME

Exhibit 5.3. Exclusionary Medical Conditions

ICD-9 Code	Condition
7588	SEX CHROMOSOME ANOM NEC*
75889	OTH CON D/T CHRM ANM NEC
7589	CHROMOSOME ANOMALY NOS
7594	CONJOINED TWINS
7595	TUBEROUS SCLEROSIS
7596	HAMARTOSES NEC
7597	MULT CONGEN ANOMAL NEC
75981	PRADER-WILLI SYNDROME
75983	FRAGILE X SYNDROME
7600	MATERN HYPERTEN AFF NB
7601	MATERN URINE DIS AFF NB
7602	MATERNAL INFEC AFF NB
7603	MATERN CARDIORESP AFF NB
76070	NOXIOUS SUBST NOS AFF NB
76071	MATERNAL ALCOHOL AFF NB
76072	MATERNAL NARCOTIC AFF NB
76073	MATERNAL HALLUCIN AFF NB
76075	COCAINE - NXS INFL FETUS
76079	NOXIOUS SUBST NEC AFF NB
7608	MATERNAL COND NEC AFF NB
7611	PREMAT RUPT MEMB AFF NB
7612	OLIGOHYDRAMNIOS AFF NB
7613	POLYHYDRAMNIOS AFF NB
7615	MULT PREGNANCY AFF NB
7617	ANTEPART MALPRES AFF NB
7618	MATERN COMPL NEC AFF NB
7640	LT-FOR-DATES W/O FET MAL*
76400	LIGHT-FOR-DATES WTNOS
76401	LIGHT-FOR-DATES <500G
76402	LT-FOR-DATES 500-749G
76403	LT-FOR-DATES 750-999G
76404	LT-FOR-DATES 1000-1249G
76405	LT-FOR-DATES 1250-1499G
76406	LT-FOR-DATES 1500-1749G
76407	LT-FOR-DATES 1750-1999G
76408	LT-FOR-DATES 2000-2499G
7641	LT-FOR-DATES W FETAL MAL*
76410	LT-FOR-DATE W/MAL WTNOS
76413	LT-DATE W/MAL 750-999G
76418	LT-DATE W/MAL 2000-2499G

Exhibit 5.3. Exclusionary Medical Conditions

ICD-9 Code	Condition
7649	FETAL GROWTH RETARD NOS*
76490	FET GROWTH RETARD WTNOS
76492	FET GROWTH RET 500-749G
76493	FET GROWTH RET 750-999G
76494	FET GRWTH RET 1000-1249G
76495	FET GRWTH RET 1250-1499G
76496	FET GRWTH RET 1500-1749G
76497	FET GRWTH RET 1750-1999G
76498	FET GRWTH RET 2000-2499G
765	EXTREME IMMATURITY
7650	EXTREME IMMATURITY*
76500	EXTREME IMMATUR WTNOS
76501	EXTREME IMMATUR <500G
76502	EXTREME IMMATUR 500-749G
76503	EXTREME IMMATUR 750-999G
76504	EXTREME IMMAT 1000-1249G
76505	EXTREME IMMAT 1250-1499G
76506	EXTREME IMMAT 1500-1749G
76507	EXTREME IMMAT 1750-1999G
76508	EXTREME IMMAT 2000-2499G
7651	OTHER PRETERM INFANTS*
76510	PRETERM INFANT NEC WTNOS
76511	PRETERM NEC <500G
76512	PRETERM NEC 500-749G
76513	PRETERM NEC 750-999G
76514	PRETERM NEC 1000-1249G
76515	PRETERM NEC 1250-1499G
76516	PRETERM NEC 1500-1749G
76517	PRETERM NEC 1750-1999G
76518	PRETERM NEC 2000-2499G
767	BIRTH TRAUMA*
7670	CEREBRAL HEM AT BIRTH
768	INTRAUTERINE ASPHYXIA*
7681	FET DEATH-ANOXIA DUR LAB
7685	SEVERE BIRTH ASPHYXIA
769	RESPIRATORY DISTRESS SYN
7702	NB INTERSTIT EMPHYSEMA
7703	NB PULMONARY HEMORRHAGE
7707	PERINATAL CHR RESP DIS
7721	NB INTRAVENTRICULAR HEM

Exhibit 5.3. Exclusionary Medical Conditions

ICD-9 Code	Condition
7722	NB SUBARACHNOID HEMORR
7725	NB ADRENAL HEMORRHAGE
7757	LATE METAB ACIDOSIS NB
7762	DISSEM INTRAVASC COAG NB
7790	CONVULSIONS IN NEWBORN
7792	CNS DYSFUNCTION SYN NB
7794	NB DRUG REACTION/INTOXIC
7795	NB DRUG WITHDRAWAL SYNDR
V310	TWIN, MATE LB-IN HOSP*
V3100	TWIN-MATE LB-HOSP W/O CS
V3101	TWIN-MATE LB-IN HOS W CS
V311	TWIN, MATE LB-BEFORE ADM
V3200	TWIN-MATE SB-HOSP W/O CS
V3201	TWIN-MATE SB-HOSP W CS
V3300	TWIN-NOS-IN HOSP W/O CS
V3301	TWIN-NOS-IN HOSP W CS
V331	TWIN NOS-BEFORE ADMISSN
V3400	OTH MULT LB-HOSP W/O CS
V3401	OTH MULT LB-IN HOSP W CS
V370	MULT BIRTH NOS-IN HOSP*
V3700	MULT BRTH NOS-HOS W/O CS
V3701	MULT BIRTH NOS-HOSP W CS
V3710	MULT BIRTH NOS-HOSP

5.2. Sampling Frame

The sampling frame for the current study, (i.e., the list from which the sample was drawn,) was created in collaboration with the data managers from each of the four HMOs participating in the study. HMO data managers first selected records from their VSD database that satisfied birth year and HMO enrollment criteria. Abt Associates then created the final sampling frame by applying additional exclusionary criteria based on child age, medical conditions, and primary care facilities. The numbers of children in the sampling frame by HMO and exposure categories are displayed in Exhibit 5.4. The exposure categories represent levels of exposure to ethylmercury from thimerosal in vaccines during the age range of one to seven months, crossed with exposure to thimerosal from receipt of hepatitis B vaccine during the first month of life.

Exhibit 5.4
Size of Sampling Frame by Exposure Category for Each HMO

	HMO-A		HMO-B		HMO-C		HMO-D		Total	
VSD Exposures	**HepB at Birth**		**HepB at Birth**		**HepB at Birth**		**HepB at Birth**		**HepB at Birth**	
Cumulative 1-7 Months	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
(0 to 62.5 μg)	226	489	224	342	53	40	5	6	508	877
(75.0 to 87.5 μg)	1122	1060	230	1272	2	3	1	10	1355	2345
(100.0 to 112.5 μg)	4376	1328	463	4762	39	321	4	17	4882	6428
(125.0 to 137.5 μg)	229	108	397	4703	20	34	1	157	647	5002
(150.0 to 162.5 μg)	104	32	26	536	202	2424	18	120	350	3112
(175.0 to 187.5 μg)	145	11	1	47	79	154	13	769	238	981
(200.0 μg & up)	0	0	0	6	3	9	21	476	24	491
Total	**6202**	**3028**	**1341**	**11668**	**398**	**2985**	**63**	**1555**	**8004**	**19236**
HMO / Grand Total	**9230**		**13009**		**3383**		**1618**		**27240**	

Note: μg = micrograms.

5.3. Sample Selection

The primary objectives of the sample selection were to obtain a) a sample with a wide distribution of exposures, and b) an analysis sample of approximately 1,200 assessed children. Due to budget constraints the target sample size was subsequently reduced to 1,100 assessed children. Power calculations had indicated that an analysis sample of this size would have more than 90 percent power to detect hepatitis B at birth and cumulative exposures in the one to seven month age range effects as small as $r^2 = 0.01$ (i.e., the effect explains one percent of total variance in the outcome measure). To obtain an analysis sample of size n=1,100, we had to select a much larger sample in order to account for sample loss due to factors such as physician refusals, geographic criteria, inability to find sampled families, additional eligibility criteria ascertained during eligibility call, and unwillingness to participate in the study.

We had originally hoped to select a sample that was balanced across the four HMOs, and across exposure categories within HMOs, and across age groups and primary care facilities within exposure categories. Perfect balance across all of those factors would eliminate the possibility of confounding on those factors. Such balance was not feasible, however, due to the sizes of the sampling frame and the distribution of exposures within each of the four HMOs. Based on the sizes and exposures across HMOs, the decision was made to allocate the sample unequally across the four HMOs. Stratified random samples were drawn from each HMO, where the strata were defined by exposure levels, with implicit stratification by age cohort and primary care facility via the use of a systematic random sampling paradigm.

The sizes of the selected samples at each HMO are displayed in Exhibit 5.5.

Exhibit 5.5
Size of Samples Selected from Each HMO by Exposure Category

	HMO-A		HMO-B		HMO-C		HMO-D		Total	
VSD Exposures	**HepB at Birth**		**HepB at Birth**		**HepB at Birth**		**HepB at Birth**		**HepB at Birth**	
Cumulative 1-7 Months	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
(0 to 62.5 μg)	226	489	224	342	53	40	5	6	508	877
(75.0 to 87.5 μg)	534	534	230	483	2	3	1	10	767	1030
(100.0 to 112.5 μg)	534	534	463	483	39	71	4	17	1040	1105
(125.0 to 137.5 μg)	229	108	397	483	20	34	1	45	647	670
(150.0 to 162.5 μg)	104	32	26	483	71	71	18	45	219	631
(175.0 to 187.5 μg)	145	11	1	47	71	71	13	45	230	174
(200.0 μg & up)	0	0	0	6	3	9	21	45	24	60
Total	**1772**	**1708**	**1341**	**2327**	**259**	**299**	**63**	**213**	**3435**	**4547**
	3480		**3668**		**558**		**276**		**7982**	

Note: μg = micrograms.

5.4. Physician, Sibling, and Out-of-Area Exclusions

After sample selection, Abt Associates sent the IDs of the sampled children to the four HMOs. Those IDs were used to generate letters to physicians informing them of which of their patients had been selected for the study and allowing the physician to ask that any child or family be removed from the sample. The HMOs tracked any families that needed to be removed from the sample based on physician requests. At HMO-B, if the child's primary care provider was unknown, the child was excluded from the sample at this point.

The HMOs also identified sibling pairs within the sample (in a few cases, three siblings were selected in the sample). The HMOs sent the IDs of the sibling groupings back to Abt Associates, where a random sample from each sibling group was selected to remain in the sample. The other member of the sibling pair (or members of the sibling group) was excluded from the sample.

At this phase, the HMOs also applied geographical exclusions whenever it was discovered that some of the sampled children lived outside of the geographic boundaries of the defined study populations. Additionally, a small number of exclusions occurred at HMO-D during this phase due to membership criteria. Exhibit 5.6 summarizes exclusions made during this phase and the sizes of the remaining samples.

Exhibit 5.6
Sample Loss Due to Physician, Sibling, and Out-of-Area Exclusions by HMO

	HMO									
	HMO-A		HMO-B		HMO-C		HMO-D		Total	
N in Selected Sample	**3480**		**3668**		**558**		**276**		**7982**	
Exclusions:	n	%	n	%	n	%	n	%	n	%
▪ Physician exclusions	31	0.9	3	0.1	0	0.0	5	1.8	39	0.5
▪ Physician Unknown	0	0.0	114	3.1	0	0.0	0	0.0	114	1.4
▪ Sibling exclusions	138	4.0	177	4.8	10	1.8	9	3.3	334	4.2
▪ Geographic exclusions	0	0.0	392	10.7	0	0.0	7	2.5	399	5.0
▪ Membership exclusions	0	0.0	0	0.0	0	0.0	8	2.9	8	0.1
Total Excluded	169	4.9	686	18.7	10	1.8	29	10.5	894	11.2
Remaining Sample	**3311**	95.1	**2982**	81.3	**548**	98.2	**247**	89.5	**7088**	88.8

5.5. Recruitment in Batches

Samples were released for recruitment in randomly selected batches. We monitored the participation rates across all four HMOs as recruitment and testing was underway. The batch release of sample allowed us to keep assessment clinics full to the maximum extent possible as the various assessment sites got up and running at various rates. The batch release also made possible the inclusion of children in later batches that were too young to satisfy eligibility criteria in earlier batches. Batches were selected as stratified random samples of the full samples, where strata were defined by exposure levels, with implicit stratification by age cohort and facility via the use of a systematic random sampling paradigm.

The batch histories are shown in Exhibit 5.7. All IDs from the two smaller HMOs (HMO-C and HMO-D) were released for recruitment in batches. At the two large HMOs, the full samples were not needed in order to achieve the overall targeted size for the analysis sample of tested children. Therefore, only a subset of the samples was released for recruitment. At each of the two large HMOs, there were small numbers of children for whom no attempt at recruitment was made because the study ended and clinics closed before the recruitment calls were made.

Exhibit 5.7
Batch History by HMO

	HMO								
	HMO-A		HMO-B		HMO-C		HMO-D		Total
N in Sample	**3311**		**2982**		**548**		**247**		**7088**
Batches:	Month	n	Month	n	Month	n	Month	n	
▪ 1st Batch	June	839	June	600	May	548	May	110	2097
▪ 2nd Batch	Jan.	250	June	220			Aug.	137	607
▪ 3rd Batch			Sept.	800					800
▪ 4th Batch			March	250					250
Total Batches		1089		1870		548		247	3754
Recruitment ended[a]		-61		-45					-106
Total Attempts[b]		**1028**		**1825**		**548**		**247**	**3648**

[a] "Recruitment ended" means clinics closed prior to recruitment call. No attempt was ever made to contact these families.

[b] "Total Attempts" are the numbers of children for whom eligibility and/or recruitment calls were made.

5.6. Recruitment and Eligibility Outcomes

Families whose physicians allowed them to be contacted by the study were sent a letter and informational brochure. A postcard was enclosed that the family could return to the HMO indicating their willingness (or refusal) to participate in the study. If no return postcard was received from a family, this mailing was followed by a telephone call from an HMO study team member, who followed a recruitment script to ascertain (a) if the mother had any questions about the materials received, and (b) if the mother was willing to be contacted by a representative of Abt Associates Inc.

Families who did not agree to be contacted by Abt Associates were asked if they were willing to provide reasons for their refusal, so that the study could track non-response data. For the families who agreed to be contacted, locating information was given to Abt Associates for follow-up to confirm the child's eligibility and the family's willingness to participate. Subsequently, a Screening Interview was conducted with each family by telephone by a trained Abt Associates interviewer. In addition to confirming that the family and child met the eligibility criteria previously discussed, additional criteria were applied: the child could not be one of a multiple birth (e.g., twin, triplet), and the biological mother had to have been at least 16 years old at the time of the target child's birth. The Screening Interview also collected information on additional criteria for participation: the biological mother had to be available to participate in the assessment, had to be mentally competent to understand the consent form and the research instruments, could be interviewed in English, and lived with the target child at least four days a week.

Exhibit 5.8 summarizes the results of the recruitment effort. The row labeled "complete" indicates children who were recruited, were determined to be eligible, and who participated in testing. Summed across the four HMOs, the total number of children that participated in the assessments was n=1,107. The row labeled "ineligible" shows the numbers of children that were determined to be ineligible during the eligibility call. The row labeled "clinic ended" shows the numbers of families that had had been contacted and who indicated a willingness to participate, but who were never assessed because data collection ended before they were scheduled to come to the clinic for an assessment. The row labeled "Refused (active)" indicates families that were contacted but who declined to participate in the study. The row labeled "Refused (passive)" shows the numbers of families that either could not be located, or had been contacted but were never assessed for any of a number of reasons, e.g. scheduling issues and failure to return phone calls.

There is little information available on the families that refused to participate. Some of the study's internal review boards (IRBs) specified that after a family had actively refused participation, no further analyses of any of the electronic data that had been available during construction of the sampling frame were allowed. At two of the sites, a

small sub-sample of families that actively refused was administered a refusal interview. Eighty-four refusal interviews were obtained from refusers from HMO-B, and 118 refusal interviews were obtained from HMO-C. Of the families that provided reasons for non-participation, 68 percent said it was due to lack of time or a busy schedule, and 13 percent gave reasons that indicated they distrusted or were ambivalent towards research.

Exhibit 5.8
Recruitment & Eligibility Outcomes by HMO

	HMO									
	HMO-A		HMO-B		HMO-C		HMO-D		Total	
Total Attempts[a]	1028		1825		548		247		3648	
Outcomes	n	%	n	%	n	%	n	%	n	%
Ineligible	182	17.7	235	12.9	78	14.2	17	6.9	512	14.0
Refused (active)	297	28.9	408	22.4	174	31.8	80	32.4	959	26.3
Refused (passive)	167	16.3	723	39.6	75	13.7	61	24.7	1026	28.1
Clinic ended	30	2.9	13	0.7	0	0.0	1	0.4	44	1.2
Complete	352	34.2	446	24.4	221	40.3	88	35.6	1107	30.3
Total	1028	100.0	1825	100.0	548	100.0	247	100.0	3648	100.0

"Total Attempts" = the numbers of children for whom eligibility and/or recruitment calls were made.
"Ineligible" = child was determined to be ineligible during eligibility call.
"Refuse (active)" = Contact was made with child's mother and she indicated that she could not or would not participate.
"Refuse (passive)" = Includes unable to locate, non-working phone number, maximum number of telephone attempts exceeded, calls not returned, willing to participate by repeated postponements to scheduled assessment, no-show at clinic.
"Clinic ended" = Clinic ended after recruitment call. These families had expressed a willingness to participate, but clinics closed prior to testing.
"Complete" = child was assessed.

5.7. Size of Analysis Sample

A total of 1,107 children were assessed for the study. After each child participated in testing, his/her medical records were abstracted and his/her mother's medical records for the period covering her pregnancy with the focus child were abstracted. Review of these data abstracted from medical charts resulted in the identification of a set of children that were ineligible for the study. In this section we describe 60 children that were excluded from the analysis data set. After applying exclusions, the analysis data set included IDs from 1,107 – 60 = 1,047 children. The 60 excluded children included:

- 1 that was excluded because the child did not receive care from the participating HMO during his/her first year of life.
- 24 that were excluded because they were low birth weight.
- 8 that were excluded because they have no weight data at any age (no birth weight, no weights at subsequent ages).
- 6 that were excluded because they had no information on prenatal exposures.
- 23 that were excluded due to exclusionary medical conditions.

One child was excluded because she/he did not receive care from the participating HMO, and we therefore did not have the necessary data on exposures. During creation of the sampling frame, low birth weight children (less than 2,500 grams) were identified via VSD diagnosis codes and were excluded. The 24 low birth weight children excluded from the analysis data set did not have the relevant VSD diagnosis codes so were not excluded during sample frame creation, but were identified as low birth weight from the data abstracted from their medical charts. Birth weights and body weights measured at subsequent ages were used in the calculation of exposure levels[6]. For the eight children with no recorded weight measurements, the postnatal measures of exposure to ethylmercury from thimerosal could not be calculated. Therefore, those children were excluded from the analysis data set. Six children were excluded because no information on prenatal exposures to mercury from thimerosal were available from either maternal medical records or from the parent interview.

During the creation of the sampling frame, records were excluded from the sample based on exclusionary medical conditions that were identified via codes in the VSD database. After chart abstractions were completed, we created a document summarizing all medical conditions identified in the abstracted chart data for any of the 1107 children. A team of five pediatricians reviewed the data and identified a set of conditions that were consistent with the exclusions applied during the creation of the sampling frame. In addition to the 24 low birth weight children, described previously, 23 additional children were excluded due to exclusionary medical conditions identified from the chart-abstracted data.

[6] The measures of postnatal exposure to ethylmercury from thimerosal were calculated as a function of the amount of mercury received and the child's weight at the time of vaccine receipt.

6. Data Sources

Data were obtained for the current study from a variety of sources, as shown in Exhibit 6.1.1. These include: (a) parent interviews; (b) records of children vaccine histories from pediatrician/clinic visits; (c) direct child assessments, (d) scoring of a language sample from each child, conducted by professionals at a specialized speech and language laboratory; (e) behavior ratings of the child by the mother and the child's primary school teacher (the latter administered by mail survey); (f) ratings of the presence of tics and stuttering, collected from the child's mother, teacher, and the child assessor at the clinic; (g) medical record abstraction, and (h) computer-automated medical data on children's health conditions and vaccinations, collected in accordance with the Vaccine Safety Datalink (VSD) system. Each data source is described below.

6.1. The Clinic Visit

Testing clinics were established at each of the participating HMOs. The clinics were organized to provide a standardized testing situation for children and a site where mothers could be interviewed without distractions. At the clinic visit, a trained interviewer conducted the Parent Interview, conducted the parent IQ test, obtained parent ratings of the child's behavior and neurological functioning, and collected any records the parent kept on the child's schedule of vaccinations. A trained child tester, who was blinded to the child's vaccine history, conducted a battery of neuropsychological assessments with the child.

As shown in Exhibit 6.1.1, the clinic visit produced data on outcomes, exposures, and covariates. Clinic visits took between 3 and 4 hours to complete, with breaks and snacks for the mother and child. For the clinic visit, children who were taking medication(s) for attention deficit hyperactivity disorder (ADHD) were asked to refrain from taking the medication 12 hours prior to the clinic visit.

Exhibit 6.1.1 **Sources for each Type of Data**		
Data	**Source**	**Method**
Child outcomes		
▪ Neuropsychological outcomes	Direct assessment	Clinic visit: assessments administered at clinic by trained child tester
▪ Speech anomalies	Direct evaluation of taped speech sample	Clinic visit/outside evaluation: taped speech sample from child evaluated at speech/language laboratory (University of Pittsburgh)
▪ Attention, executive functioning, and behavior regulation at home	Parent rating	Clinic visit: parent ratings as part of Parent Interview
▪ Attention, executive functioning, and behavior regulation at school	Teacher ratings	Mail questionnaire: Sent out to child's teacher
▪ Tics and stuttering	Parent rating	Clinic visit: parent ratings as part of Parent Interview
	Teacher rating	Mail questionnaire: Sent out to child's teacher
	Assessor rating	Clinic visit: assessor rating as end of assessments
Exposures		
▪ Child	Medical report	Data abstraction: data from VSD computerized database
		Clinic visit: vaccination record brought by parent into clinic visit
	Parent report	Clinic visit: Parent Interview questions on child's receipt of vaccinations
	Child medical records	Data abstraction: Medical record data
▪ Mother	Mother medical records	Data abstraction: Medical record data
	Parent report	Parent interview
Covariates		
▪ Maternal IQ	KBIT (Kaufman Brief Intelligence Test)	Clinic visit: administered at clinic by trained interviewer
▪ Characteristics of child, family, home	Parent report	Clinic visit: Parent Interview
▪ Exposure to other toxins	Parent report	Clinic visit: Parent Interview
▪ Medical history	Child medical record	Data abstraction: Medical record data

6.1.1. Clinic Staff

Two kinds of staff operated the clinic sessions: the Clinic Managers (parent interviewer) Child Assessors. Clinic Managers were college graduates who had extensive experience either in office management or in coordinating research studies. These staff people were responsible for administering the informed consent, conducting the Mother Interview (described in a subsequent section), providing guidance to the mother for completing the self-administered rating scales, conducting the mother IQ measure, and performing all of the administrative tasks that were necessary for the coordination of the data collection. The Clinic Manager scheduled all clinic visits, sent data to Abt Associates, ordered supplies, and acted as coordinator on site.

Child Assessors had at least a Master's degree, some had PhDs, and all had training and experience in testing children. These staff were critical to the study and were extensively trained to be proficient in the administration and scoring of the child tests. In addition, they were responsible for making sure that the data that they collected were sent to the appropriate people for subsequent review and processing.

In addition to the two types of clinic staff, a third type of professional provided overall supervision of the child assessors. At each HMO, the study hired licensed Clinical Psychologists who were trained to review the administration and scoring of the tests. The Clinical Psychologists double-scored the data provided by the Child Assessors. Child Psychologists reviewed all child assessment data (previously scored and entered by the Child Assessors) for completeness and accuracy and were responsible for interpretation of the tests and for writing the letters to the parents informing them of their children's results. Clinical Psychologists also were available to parents to discuss their children's scores. Furthermore, a Clinical Psychologists was on call each time the clinic was in session, to provide backup support for the Child Assessors and to be available for consultation on the phone or in-person in case of emergencies

6.1.1.1. Training and Quality Control

One of the most important activities of this project was the training and testing of Clinic Managers and Child Assessors for inter-rater reliability. This training was conducted by experienced neuropsychologists. Clinic Managers and Child Assessors had to pass two kinds of reliability testing. First, they were tested for administrative fidelity during training, based on mock scripts and were tested for scoring accuracy using written scoring tests. At training, Clinic Managers and Child Assessors had to pass tests of administration and scoring for all of the instruments for which he/she was responsible. Any Clinic Manager or Child Assessor who did not pass these tests was not hired for the study.

Training and reliability checks continued for Clinic Managers and Child Assessors in the field. Prior to the actual data collection, pilot testing with non-study families was conducted to test the data collection protocol, check timing of clinic assessments and total clinic visit, and to further establish reliability of the Clinic Managers and Child Assessors. Clinic managers audiotaped these pilot interviews and tests and sent these tapes along with their scored tests and edited interviews to Abt staff for review.

Each Child Assessors was observed conducting a test session by a Consulting Psychologists with pilot test children. Consulting Psychologists were given specific criteria to use for monitoring the Child Assessors during each subtest. They were asked to make judgments about each Child Assessor's fidelity to the test administration based on the project training and the assessor's ability to establish rapport with the child during testing.

6.1.2. Child Assessments

At the clinic, each child was administered a battery of 14 tests comprising 26 subtests and covering nine developmental domains. Additional measures of child outcomes were obtained from parent interview and teacher surveys (described subsequently) and from child assessor ratings of the presence of tics and stuttering. The battery of assessments is summarized in Exhibit 6.1.2. Note that one of the measures, the Goldman-Firstoe, was

scored outside of the clinic in a language laboratory under the supervision of Dr. Tom Campbell of the University of Pittsburgh.

Exhibit 6.1.2
Child Assessment Battery

Measurement Instrument	Subtest(s)/Constructs Tested	Outcome(s)	Data Collection Method
Speech and Language			
Boston Naming Test	Naming vocabulary	Total number of correctly-named pictures	Direct assessment at clinic
NEPSY (2 subtests)	Language subtests: • Speeded Naming (rapid access to/production of names of recurring colors, sizes, shapes) • Comprehension of Instructions (process/respond quickly to verbal instructions of increasing syntactic complexity)	 Total score (based on Time to Completion and Total Number Correct) Total correct responses	Direct assessment at clinic
Clinical Evaluation of Language Fundamentals–Third Edition (CELF-3) (2 subtests)	Expressive language subtests: • Formulated Sentences (formulation of simple, compound, complex sentences) • Recalling Sentences (recall/ reproduction of sentence surface structure as a function of syntactic complexity)	Total score based on completeness of sentence Total score based on accuracy of sentence recall	Direct assessment at clinic
Goldman-Fristoe 2 Test of Articulation (GFTA-2)	Sounds-in-Words (spontaneous speech production of single words)	Total number of articulation errors	Audio recording of child sent to speech laboratory for scoring on articulation.
Iowa Scale for Rating Severity of Stuttering	Speech/language dysfluencies	Parent rating (1-7) Clinical assessor rating (1-7) Teacher rating (1-7)	Rating by parent and clinical assessor at the clinic visit Rating by teacher via mail survey
Verbal Memory			
California Verbal Learning Test—Children's Version (CVLT-C) (5 subtests)	Immediate Free Recall Short Delay Free Recall Short Delay Cued Recall Long Delay Free Recall Long Delay Cued Recall	Total number correctly recalled Total number correctly recalled Total number correctly recalled Total number correctly recalled Total number correctly recalled	Direct assessment at clinic
Children's Memory Scale Stories 1 and Stories 2 (2 subtests)	Immediate Recall of connected, meaningful text Delayed Recall of connected, meaningful text	Number correctly recalled story units Number correctly recalled story units	Direct assessment at clinic
Achievement			
Woodcock-Johnson Psycho-Educational Battery-Revised: Tests of Achievement	Letter-Word Identification (phonemic awareness--ability to match a rebus with actual picture; ability to identify isolated letters and words)	Total number correct converted to "W" [Rasch logit score]	Direct assessment at clinic

Exhibit 6.1.2
Child Assessment Battery

Measurement Instrument	Subtest(s)/Constructs Tested	Outcome(s)	Data Collection Method
Fine Motor Coordination			
Grooved Pegboard (2 subtests)	Manipulative dexterity- Dominant hand Manipulative dexterity- Non-dominant hand	Total time to completion: dominant hand Total time to completion: non-dominant hand	Direct assessment at clinic
Finger Tapping Test (2 subtests)	Manipulative dexterity- Dominant hand Manipulative dexterity- Non-dominant hand	Maximum number of taps: dominant hand Maximum number of taps: non-dominant hand	Direct assessment at clinic
Visual Spatial Ability			
Stanford-Binet Intelligence Test Copying subtest	Visuomotor coordination (reproduce designs with blocks/ copy simple and complex geometric patterns from pictures on cards)	Total number correct	Direct assessment at clinic
Attention /Executive Functioning			
Gordon Diagnostic System (GDS) (2 subscores)	Vigilance Task: ability to respond accurately and quickly to presentation of paired numbers on screen	Number correct responses Number commissions	Direct assessment at clinic
WISC III Digit Span subtest (3 subscores)	Memory for digit strings	Score for digits forwards Score for digits backwards Combined score	Direct assessment at clinic
Behavior Rating Inventory of Executive Function (BRIEF)	Metacognition Index (child's ability to plan, organize, sustain future-oriented problem solving in working memory)	Parent rating: Total score Teacher rating: Total score	Separate ratings by child's teacher (mail survey) and parent (parent interview)
Behavior Regulation			
Conners' Rating Scales—Revised (2 subscores)	Inattentive (cluster of symptoms on DSM-IV diagnosis of ADHD--predominantly inattention) Hyperactive-Impulsive (cluster of symptoms on DSM-IV diagnosis of ADHD--predominantly hyperactivity-impulsivity)	Parent rating: Total score Teacher rating: Total score	Separate ratings by child's teacher (mail survey) and parent (parent interview)
Behavior Rating Inventory of Executive Function (BRIEF)	Behavioral Regulation Index (shifting of cognitive set and modulating emotions and behavior to achieve goal)	Parent rating: Total score Teacher rating: Total score	Separate ratings by child's teacher (mail survey) and parent (parent interview)
Tics			
Yale Global Tic Severity Scale (scores for 2 types of tics)	Motor tics Phonic tics	Clinical assessor report of motor tics/phonic tics during assessment Parent report on motor tics/phonic tics shown by child in prior 7 days	Ratings by parent as part of parent interview at clinic and by child assessor at end of clinic visit

Exhibit 6.1.2
Child Assessment Battery

Measurement Instrument	Subtest(s)/Constructs Tested	Outcome(s)	Data Collection Method
General Intellectual Functioning			
WASI (4 subtests resulting in Verbal and Performance scores)	Verbal subtests: • Vocabulary (oral definition of orally-presented words) • Similarities (state rule for how two objects or concepts are similar)] Performance subtests: • Block Design (2-dimensional geometric patterns to be replicated with two-color cubes) • Matrix Reasoning (choosing piece of matrix that best completes the designs—untimed; taps analogic reasoning, spatial visualization, visuospatial reasoning)	Verbal IQ standard score (M=100, SD=15) Performance IQ standard score (M=100, SD=15) Full scale IQ standard score (M=100, SD=15)	Direct assessment at clinic

6.1.3. Parent Interview

The parent interview was administered to the child's biological mother during the clinic visit. The interview produced detailed data on:

- Family structure and demographics
- Family educational history
- Home characteristics
- Prenatal medical care
- Events and exposures during pregnancy with focus child
- Events and exposures during infancy
- Child's use of medications
- Child's developmental diagnoses
- Maternal developmental diagnoses

To obtain a measure of the mother's IQ, the Kaufman Brief Intelligence Test (KBIT) was administered to each mother by the clinic coordinator.

Mothers were also asked to bring their child's immunization records from their personal files to the clinic visit.

As part of the parent interview, the mother rated the child's behavior at home, using the Conners Rating Scales and the Behavior Rating Inventory of Executive Function (BRIEF).

Mothers were also asked whether the child had exhibited any stuttering or tics in the seven-day period leading up to the clinic visit.

6.2. Teacher Mail Survey

The child's primary school teacher also was asked to (a) rate the child's behavior using Conners' Rating Scales and the BRIEF , which produced measures of children's attention/executive functioning, and behavior regulation, and (b) indicate whether the child exhibited stuttering at school in the seven-day period leading up to date that the teacher completed the child ratings. This information was obtained from teachers via mail-return questionnaire.

6.3. Medical Record Abstractions

Data from both the mother's and the child's medical records was abstracted by trained record abstractors at each HMO (typically, HMO medical staff). The abstraction were developed to collect the following information from the maternal medical record: 1) pregnancy history; 2) complications, illness, procedures and treatments during the pregnancy with the target child; 3) procedures or complications of labor and delivery, including method of delivery and any drugs administered during labor; 4) maternal hepatitis B antigen status, receipt of Rhogam (or other Rh(D) immunoglobulin), and

receipt of any vaccines during pregnancy with target child; and 5) maternal medical history for developmental outcomes.

Data abstracted from the child's medical records included: 1) perinatal data, such as gestational age, birth weight, birth length, head circumference at birth, Apgar scores and birth plurality; 2) abnormal conditions and clinical procedures relating to newborn; 3) infant medications; 4) all receipts of any vaccines or immune globulins; 6) all receipts of antibiotics; 7) developmental delays or conditions and psychiatric conditions, including date of the first mention of the condition in the medical chart, date of first prescribed medications, date of first referral, and type of service provider; and 8) medical conditions, such as lead poisoning and anemia/iron deficiency, including date of first mention in the medical chart.

Each medical record abstractor attended a half-day training session that covered the background and purpose of the study; medical abstraction forms for the mother and child; working with the clinician to obtain copies of medical release forms of the clinically assessed children in order to obtain medical records; maintaining subject confidentiality; transmittal of data to Abt's central office; and quality assurance.

All medical abstraction data were double entered by a professional data-entry house.

6.4. VSD Computer-Automated Data

The computer-automated data, collected and maintained in accordance with the Vaccine Safety Datalink (VSD) system (Chen et. al, 2000), were provided to the study from each of the four participating HMOs. These data were used in the creation of the sample frame (see Chapter 5) and used in the analysis phase to create measures of exposure and covariate measures. These data sets included information on child's sex and date of birth; vaccination information including date and type of vaccine received, vaccine manufacturer and lot number and indicators of whether vaccines were received inside or outside of the HMO; inpatient and outpatient medical care information including ICD-9 codes and dates; and information about child's birth including gestational age, birth weight, apgar score, and mother's date of birth.

7. Measures

7.1. Outcome Measures

7.1.1. Outcomes Measured on Continuous Scales

Thirty-five of the 42 outcomes in this study were measured on a continuous scale. Each of these 35 outcome measures was obtained from administration of commercially available assessment instruments and in each case we followed the test publisher's instructions for administering the assessments and assigning scores. After the outcome measures were entered into a computerized database, each measure was subjected to a series of checks prior to its inclusion in the analysis data set. A record identified in any of the following checks triggered a process of looking up the original hand-recorded assessment form, recalculating summary scores (if applicable), and checking against the value shown in the computerized database:

1. Either raw or scale score outside the range of values indicated in the test's technical manual.
2. Child had either a raw score but a missing scale score, or a scale score but a missing raw score.
3. Standardized (studentized) residuals from model with scale score regressed on raw score exceeds cut-off level[7].
4. Standardized (studentized) residuals from model with scale score regressed on age and sex exceeds cut-off level.
5. Standardized (studentized) residuals from model with raw score regressed on age and sex exceeds cut-off level.
6. Very unusual value identified in scatter-plot of raw score versus age.
7. Very unusual value identified in scatter-plot of scale score versus age.

7.1.2. Dichotomous Outcomes: Tics and Stuttering

Unlike the previously described continuous outcome measures, the tics and stuttering outcomes were not obtained from commercially available assessment batteries. As will be described below, assessments of the presence of tics and stuttering among study participants were obtained from multiple sources. As part of determining the most valid way to construct the child outcomes for tics and stuttering, we consulted with a speech and language expert, Dr. Thomas Campbell of the University of Pittsburgh. We reviewed our tics and stuttering data with Dr. Campbell and made final decisions about how to construct the outcomes. The decisions regarding the creation of the tics and stuttering measures were made prior to any linking of exposure and outcome data.

[7] We used a cut-off suggested by Bollen and Jackman (1990) to identify distance outliers (i.e., highly unusual observations). Their suggested cutoff is the quantile of a t-distribution corresponding to probability equal to $\alpha/2n$ and degrees of freedom equal to the number of observations minus 1. With alpha set to 0.05 and n equal to 1,047, the value of the cut-off level is +/- 4.08.

7.1.2.1. Tics

The study collected information on children's tics from two sources: the parent reported on any tics shown by their child currently (in the seven days prior to and including the day of assessment) or ever, and the clinical assessor reported on any tics manifested by the child during the testing session. Parents were given instructions on how to recognize phonic and motor tics, and were asked to indicate whether the child exhibited each type of tic. The clinical assessors were provided with standardized training on how tics might be manifested in children.

Four binary outcome variables were created to indicate the presence of tics:

- Any motor tic observed by the clinical assessor at the time of the testing;
- Any phonics tic observed by the clinical assessor at the time of the testing;
- Any current motor tic reported by the child's mother;
- Any current phonics tic reported by the child's mother.

1. Separate tic variables were constructed for the assessor and the parent for three reasons:

- The two reporters did not agree on which children had tics. Although both the parents and the assessors identified 95 children as having motor tics, only 22 of the 95 children were identified by both having motor tics. The assessors identified 73 children as having motor tics that were not identified by the parents, and the parents identified a different 73 children as having motor tics that were not identified by the assessors. Similarly, assessors identified 76 children as having phonic tics, the parents identified 107 children as having phonic tics, and only 17 children were identified as having phonic tics by both assessors and parents.
- There are logical reasons to believe that the two reporters might identify different children as having tics, based on the fact that parents have a more thorough knowledge of their child in various types of situations but the assessor, unlike the parent, was observing the child in a potentially stressful situation where any tics might be likely to appear.
- In previous studies using tics as a child outcome, physician reports are the commonly used basis for identifying tics. Since physician reports of tics are likely to reflect parent report rather than direct physician observation of tics, we wanted to maintain a tic variable that comes closest to approximating the reporting basis in the literature.

2. Our rationale for constructing separate variables for motor and phonics tics rather than combining them into a single binary variable (any type of tic or none) is as follows. When clinicians discuss tics, they typically are referring to motor tics. In order to maintain a variable that links most directly to the way the field thinks about tics, we decided to create separate variables for motor and phonics tics.

3. Although both the parent and the assessor could report multiple types of motor or phonics tics, we constructed a binary variable (any tic) rather than a count of tics, since we believed that the actual number of tics identified may not have been reliable.

4. Parents reported both any current motor or phonics tics and any tics that the child *ever* manifested. We decided to construct the tic variables for parents based only on their reports of current tics. This is based on the recommendation of our technical expert that transient tics are less likely to be severe or notable and therefore should not be considered.

7.1.2.2. Stuttering

The study collected information on children's stuttering from three sources: parent report on whether the child currently stuttered; the clinical assessor report on any stuttering exhibited by the child during the testing session; and reports from the children's teachers on any stuttering by the child while in school. Each reporter was asked to indicate the severity of the child's stuttering on a 7-point scale, where 1 = very mild and 7 = very severe.

Three binary outcome variables were created to indicate the presence of stuttering:

- Any stuttering observed by the clinical assessor during the testing;
- Any stuttering reported by the parent;
- Any stuttering at school reported by the teacher.

1. Reports on stuttering from parents, clinical assessors, and teachers were kept separate, to maintain parallelism with the tic variables.

2. A child was identified as having a stutter only if the reporter indicated the severity of the stuttering was at least 2 on the 7-point scale, where 2 = mild. This means that no stuttering and very mild stuttering form the "0" value on the binary stuttering variable and mild to very severe (2 and above) form the "1" value. This criterion was based on a recommendation by the technical expert, who felt that a child rated as having very mild stuttering probably does not have a stuttering disorder.

7.2. Measures of Postnatal Exposure to Ethylmercury

7.2.1. Introduction to the Vaccination Histories File

Three sources of postnatal vaccination data (computer-automated, chart abstraction, and parent provided immunization records) were combined to create a *Vaccination Histories File.* This file contains the vaccination histories of the n=1,047 children in the analysis data set. Each row of the Vaccination Histories File represents a record of a vaccine received on a particular day. Thus, the file has many records per child. The file includes each child's "resolved vaccine history", and also includes the raw, original, un-cleaned vaccine data from each of three data sources. The resolved vaccine histories were obtained from cleaning the raw, original data and resolving any discrepancies among the three data sources and any discrepancies between the records and recommended childhood vaccination schedules. Cumulative exposure amounts were calculated from each child's resolved vaccine history. Data cleaning procedures are described subsequently.

Exhibit 7.2.1.1 shows an example resolved vaccine history for one child. The column "Res_Vacdays1" shows the child's age in days at the time of each vaccine receipt. The exhibit shows that the child received vaccines on the day she/he was born (day 1), and at ages 63, 126, and 183 days. The next three columns to the right show the type of vaccine received (Res_VacType), the manufacturer (Res_Mfr), and the ethylmercury amount contained in each vaccine (MercAmt). Additional detail is provided subsequently in this document regarding vaccine types and the assignments of mercury amounts associated with each receipt. The column labeled "RecptWtKG1" shows the child's weight (in kilograms) at the time of vaccine receipt. And the final column (Amt_wt1) shows the mercury amount for each receipt divided by the child's weight at the time of the vaccine receipt. To create the exposure variables used in the analyses, the values of "Amt_wt1" were summed over particular age ranges.

Exhibit 7.2.1.1 Example of a Resolved Vaccine History

ChildID	Res_Vacdays1	Res_VacType	Res_MFR	MercAmt	RecptWtKG1	Amt_wt1
0001	1	HepB	SKB	12.50	3.65	3.42
0001	63	DTP	CON	25.00	5.90	4.24
0001	63	HIB	MSD	12.50	5.90	2.12
0001	63	HepB	SKB	12.50	5.90	2.12
0001	63	Polio	LED	0.00	5.90	0.00
0001	126	DTP	CON	25.00	7.17	3.49
0001	126	HIB	MSD	12.50	7.17	1.74
0001	126	Polio	LED	0.00	7.17	0.00
0001	183	DTP	CON	25.00	8.51	2.94
0001	183	HepB	SKB	12.50	8.51	1.47
0001	183	Polio	LED	0.00	8.51	0.00

7.2.2. Overview of Steps from Raw Data to Creation of Analysis Variables

Data on early childhood exposure to ethylmercury from thimerosal containing vaccines and immune globulins were obtained from three sources: From computer-automated data files, from abstractions of each child's medical records, and from records provided by parents at the time of the parent interview. An overview of the data processing steps from the receipt of raw data files to the creation of the exposure variables used in analyses is as follows:

1. The master list of study IDs was merged to each of the three vaccine files (computer-automated, chart abstraction, and parent provided immunization records). Any problems with ID discrepancies were resolved at this stage. Each of the three files contained many records per child ID, where each record represented a single vaccine receipt. Each file contained fields for child's ID, type of vaccine received, and either the date the vaccine was received or the child's age in days at the time of vaccine receipt. The computer-automated and chart abstracted data sets also contained fields for vaccine manufacturer and lot number. The master list of study IDs contained each child's ID and date of birth.
2. For each of the three files (chart, computer automated, parent provided immunization records) a new *VacType* (vaccine type) variable was created, where the possible values taken by the variable, and the spelling of each vaccine type were standardized across all three files. For example, in the computer-automated data set, the codes 08, 43, and 45 took the value "HepB" on the *VacType* variable. In the chart data set, entries originally recorded as "HEP B", "HEP-B", "HEP B RECOMB", and several others were assigned the value "HepB" on the *VacType* variable. In the parent report data set, entries originally coded as "hepb", "HepB", and several others were assigned the value "HepB" on the *VacType* variable. The common coding of the *VacType* variable made possible the merging and alignment of the three data sources on receipts of particular types of vaccines. All

recodes were discussed and confirmed during weekly conference calls with the whole study team (the team included CDC staff, principal investigators from each of the HMOs, many of whom are pediatricians, data managers from each of the HMOs, and Abt staff).

3. For the chart abstraction and parent provided immunization records files, each child's age in days corresponding to each vaccine receipt was calculated. The computer-automated data set was delivered to Abt Associates with a field for child's age in days at time of vaccine receipt.
4. The three files were merged by child's ID, child's age in days at time of vaccine receipt, and vaccine type.
5. The next step was to resolve discrepancies in vaccine histories. Discrepancies included differences between the three data sources regarding the receipt of a vaccine on a particular day, or between the vaccine history indicated in the data set and the recommended vaccine schedule. An example of the former is a case where the medical chart abstraction data set indicated receipt of hepatitis-B vaccine for a child on day 1 (i.e. on day child was born), but where the computer-automated data showed no receipt on that day, and where the parent did not provide a vaccine record. An example of the latter is when a particular data source (e.g. chart or computer automated) indicated receipt of two full series of DTaP, HIB, and HepB only two days apart. Receipt of two full series separated by only two days represents a major discrepancy from recommended vaccine schedules. It is exceedingly unlikely that a child would have received these series two days apart. It is much more likely that the duplicate records are due to clerical errors. Resolution of discrepancies was a major task and is considered in greater detail in Section 7.2.3. This data cleaning phase focused exclusively on vaccines and immune globulins received during the age range from birth to one year. Resolution of discrepancies resulted in a "resolved vaccine history" for each child.
6. In the next step we assigned a mercury exposure amount corresponding to each vaccine receipt shown in each child's resolved vaccine history. For example, polio vaccine receipts were assigned an exposure amount equal to zero micrograms of ethylmercury, hepatitis-b vaccines were assigned an exposure amount equal to 12.5 micrograms of ethylmercury, and HIB vaccines were assigned values of 0, 12.5, or 25 micrograms depending on the type of HIB vaccine received. Additional details on the exposure amounts corresponding to each vaccine type are provided in Section 7.2.4.
7. Next, we needed to obtain the child's weight (in kilograms) corresponding to each age (in days) that the child received a vaccine. For most records the process was straightforward because children's weights are often recorded in medical records at the same time that vaccines are administered. In some cases, however, the data on children's weights were incomplete or did not align perfectly to the dates of vaccine receipt. When a vaccine receipt did not have a corresponding weight, one of two methods was used to impute a weight. If there were recorded weights before and after the vaccine receipt, then linear interpolation was used to predict the child's weight on the day of vaccine receipt. If there were no recorded weights after the vaccine receipt, then all of the child's recorded weights were used in a

growth curve model to predict the child's weight at the time of the vaccine receipt. The predictions from the growth curve models aligned very closely with the growth curves published in the *2000 CDC Growth Charts for the United States: Methods and Developments*. Children with no recorded weights were excluded from the analysis data set.

8. For each vaccine receipt, the mercury exposure amount (expressed as micrograms of ethylmercury contained in the vaccine) was divided by the child's weight (in kilograms) at the time of vaccine receipt, resulting in a measure of *exposure per kilogram per vaccine receipt*. For example, if a child weighed 8 kilograms at the time of receipt of a vaccine containing 12.5 micrograms of ethylmercury, then the value on this variable corresponding to this vaccine receipt would be equal to 12.5 / 8 = 1.56 micrograms per kilogram.
9. Finally, for each child, the variables representing *exposure per kilogram per vaccine receipt* were summed over all vaccines and immune globulins received within each of three age ranges (0 to 7 months; 0 to 1 month; 1 to 7 months) to produce the following three variables that were used in the analytical models:
    - *Exp07mos* = "Exposure zero to 7 months" = Exposure per kilogram per vaccine receipt summed over all vaccines and immune globulins received during the age range from birth to seven months of age (1 to 214 days).
    - *HepB* = "Exposure zero to 1 month" = Exposure per kilogram per vaccine receipt summed over all vaccines and immune globulins received during the age range from birth to one month of age (1 to 28 days). This variable was named "*HepB*" because all vaccine received during this age range were either hepatitis-b vaccines or hepatitis-b immune globulins.
    - *Exp17mos* = "Exposure one to 7 months" = Exposure per kilogram per vaccine receipt summed over all vaccines received during the age range from one to seven months of age (29 to 214 days).

Several additional exposure variables were created and used in models to estimate exposure effects when the receipt of thimerosal-containing vaccines coincided with antibiotic treatment. Those variables are described in the section titled "Concurrent Antibiotics-by-Exposure Interaction Models" (Section 9.2.6).

Three additional variables were created that were not used in the analytical models, but were used for descriptive purposes. These three variables were similar to those defined above, except that there was no division by the child's weight at the time of vaccine receipt. They are:

- Amt07mos = "Amount zero to 7 months" = Amount of ethylmercury per vaccine receipt summed over all vaccines and immune globulins received during the age range from birth to seven months of age (1 to 214 days).
- Amt01mos = "Amount zero to 1 month" = Amount of ethylmercury per vaccine receipt summed over all vaccines and immune globulins received during the age range from birth to one month of age (1 to 28 days).
- Amt17mos = "Amount one to 7 months" = Amount of ethylmercury per vaccine receipt summed over all vaccines received during the age range from one to seven months of age (29 to 214 days).

7.2.3. Data Cleaning for Child Vaccination Histories

Data on early childhood exposure to Thimerosal from vaccines and Hepatitis-B immune globulins were obtained from three sources: From computer automated data files[8], from abstractions of each child's medical records, and from records provided by parents at the time of the parent interview. Section 7.2.2 provided an overview of the data processing steps from the receipt of raw data files to the creation of the exposure variables. The purpose of the current section is to provide detail on the data cleaning procedures used to derive a "resolved vaccine history" for each child. We use the term "resolved vaccine history" to mean the final vaccine history for a child after having resolved any discrepancies among the three data sources regarding the receipt of a vaccine on a particular day, or between the vaccine history indicated in the raw data set and the recommended vaccine schedule.

In the sections that follow we describe each of several data cleaning procedures that were applied to the combined data set. Explanations of these procedures are accompanied by examples. The data cleaning procedures were developed in close consultation with data managers and investigators at each of the four participating HMOs, and with investigators at the CDC. This team included several pediatricians with firsthand experience in administering childhood vaccinations and in-depth knowledge of vaccination policies and practices used during the time period covered by the study. The team also included data managers and analysts from the HMOs who had a great deal of experience in the use of vaccination data for research purposes.

In a process spanning several months, the entire team scrutinized countless records to help develop and validate the data cleaning procedures. As computer automated cleaning algorithms were developed, samples of resulting vaccine histories, shown along with the raw data from each of the three data sources, were sent out to all team members and were discussed during weekly telephone conferences. Near the end of the process, in order to validate that the computerized algorithms did not generate any unexpected results, Abt staff scrutinized printouts showing the resolved histories and the raw data for every child in the data set.

[8] Each HMO that participated in the study maintains computer-automated vaccine records for administrative use and for research purposes. These computer-automated files are part of the Vaccine Safety Datalink system.

7.2.3.1. Step 1: Preliminary Vaccine History

After combining vaccination data from all three sources (chart, computer-automated, parent provided immunization records) we preliminarily assumed, when a vaccine receipt appears in one or more, but not all three data sources, that the vaccine was received by the child. In other words, a vaccine did not need to appear in all three data sources in order to be counted. As will be shown later, the assumption is preliminary because subsequent cleaning rules may remove one or more of the vaccines from the resolved history. An example of the application of this assumption is shown in Exhibit 7.2.3.1, where the resolved vaccine history includes a hepatitis-B vaccine receipt at age 2-days. The right-hand panel of the exhibit shows the vaccine records from the chart, computer-automated and parent provided immunization records data sets. The relevance of the columns for manufacturer and lot number will become apparent in subsequent examples. As shown in the exhibit, this receipt was indicated in the chart data, but was not present in the computer-automated data. There were no parent provided immunization data for this child. The left-hand panel of the exhibit shows the resolved vaccine history for ID # 258. This child received hepatitis-B vaccines at ages 2, 54, and 282 days, and several other vaccines on ages 60, 178, and 233 days. The resolved vaccine history includes only vaccines received during the age range spanning from birth to 365 days, i.e. from age (in days) = 1 to 365. The columns of the middle panel of the exhibit are for indicators for decision rules. None of those rules were applied in this example, but will be discussed in a subsequent section.

7.2.3.2. Step 2: Application of 30-day and 15-day Algorithms

A set of algorithms was developed to detect duplicate records of receipts of HepB, Hib, DTP, DTaP, combined DTP-Hib, combined DTaP-Hib, and polio vaccines within the first year of life. Since polio vaccines did not contain thimerosal, it was not strictly necessary to include them in the cleaning processes, but they were included nonetheless. However, for the other vaccines listed above, failure to identify and remove duplicate records from the resolved vaccine history would result in an overestimate of a child's mercury exposure. Checks for other, less commonly administered childhood vaccines are described in a subsequent section of this document.

For all of the vaccine types listed above, except HepB, the algorithms were based on an assumption that two receipts of a single type of vaccine separated by a period of 30 days or less, represents a major discrepancy from the recommended vaccination schedule. When such cases were detected, the algorithms marked one of the assumed duplicates for removal, and retained the other in the resolved vaccine history. The process for deciding which to keep and which to remove is described subsequently. These algorithms were created with the full awareness that, in the rare instance that a child was mistakenly administered one or more of these vaccines twice in a period of less than 30 days, the application of the algorithm would result in an underestimate of the child's actual exposure. However, there was consensus among the study team that those instances were

expected to be exceedingly rare, whereas duplicate entries of the same vaccine were known to be common. Therefore, the algorithms focused on solving the common problem, hence preventing overestimates of exposure, while simultaneously, in rare instances, potentially causing underestimates.

The assumptions underlying the algorithms for HepB were similar to those described above, except that, when one of the receipts is a HepB that was received in the first month of life, it is plausible for two doses to be separated by a period of less than 30 days. This occurs, for example, in cases when a child receives a late birth dose of HepB, or an early month-1 dose of HepB. Examples include records of children who received HepB vaccinations on days 1 and 29, on days 15 and 43, and on days 2 and 31. The team considered it to be implausible to receive two doses within a period of 15 days or less when one of the receipts occurs in the first month of life, so the algorithm was programmed accordingly. When neither receipt fell within the first 30 days of life, the 30-day algorithm as previously described was applied for HepB vaccinations.

Detecting duplicate records for DTPs and Hibs was complicated by the fact that some discrepancies were caused by situations such as a record of a combined DTP-Hib vaccine in one data source, but separate DTP and Hib vaccines in another source, or entry of a DTP in one source, but entry of a DTaP in another source. The algorithms were designed to detect duplicates in all permutations of individual DTP, DTaP, DT TD, TT, experimental DTaP, and HIB vaccines, and combined DTP, DTaP, and HIB vaccines.

When duplicate records were detected, a set of decision rules was applied to determine which of the two records should be omitted and which should be retained in the resolved vaccine history. The first decision rule was dependent on which of the two records had non-missing information on manufacturer and/or lot number. The record containing information on manufacturer and lot number was deemed to be more reliable and was therefore retained. In order to facilitate the comparisons, a ***manufacturer and lot number information score*** was computed for each record as follows. The combined data set included two variables from the chart data set that listed vaccine manufacture and lot number, and two additional variables listing vaccine manufacture and lot number from the computer-automated data set. For each of those four variables, we created a corresponding dummy variable that took the value “1” if the manufacturer or lot number was non-missing, and took the value “0” otherwise. We then calculated the sum of the four dummy variables to obtain the *manufacturer and lot number information score* for each vaccine record. Possible values on this score were 0, 1, 2, 3, or 4. If one of the two duplicates had a higher score, it was retained, and the other was omitted.

Exhibit 7.2.3.2 shows an example where combined DTP-HIB vaccines were retained on days 121, and 185, while separate DTP and HIBs were omitted from the same days because the former had non-missing manufacturer and lot number, while the latter did not. This example also shows same-day-duplicate HIBs that were omitted on day 63. In the “decision rules” columns of the exhibit, “1”s indicate omitted duplicates.

In cases of a tie on the *manufacturer and lot information score*, a second decision rule was implemented. Many duplicates were caused by slight discrepancies between the computer-automated and Chart data sources on the child's age in days at the time of vaccine receipt. If either of the two duplicates matched the parent provided data regarding the age in days at time of vaccine receipt, and the other did not, the record with the match in the parent data set was retained and the other was omitted.

An example of the application of the second decision rule is presented in Exhibit.7.2.3.3 where HIB and polio vaccines recorded on day 117 were omitted from the resolved history because the same vaccine types were recorded on day 120, and the latter had matching parent provided data. This exhibit also has an example of an application of the first decision rule. The exhibit shows DTaPs on days 62, 120, and 174 that were omitted because the records of DTPs on the same days had non-missing manufacturer and lot numbers.

Finally, if neither of the two previous rules produced a decision of which to retain and which to omit, then one was chosen at random to retain, and the other was omitted. An example is presented in Exhibit 7.2.3.4, where records of HIB and polio receipts on day 130 were omitted, but records of the same vaccines received on day 131 were retained in the resolved vaccine history. The choice of which to omit and which to retain was random.

7.2.3.3. Step 3: Check, Verify or Fix

This section summarizes a set of checks that were carried out on the children's vaccine histories to identify potential errors. Vaccine histories identified by this set of checks were scrutinized by the study team during weekly phone conferences and decisions were made either verifying that the history was already correct, or that fixes were needed. Often a decision was made that a child's medical records should be pulled and studied for clues on how to resolve potential discrepancies. The process of checking and fixing was iterative, such that after programming code was written and executed resulting in a change in a set of resolved vaccine histories, the set of checks was run again. The programming code used to make changes was applied only to the resolved vaccine history. The original data from the chart, computer-automated, and parent immunization records sources were never changed. A summary of the set of checks is as follows:

1) Verify that there are no two receipts of vaccines of a single type separated by less than 30 days, unless one is a HepB that was received during the first month of life.

2) Check for any receipts shown as having occurred before the child was born.

This type of error was caused by incorrect date entries. These errors were rectified by examination of the child's full vaccine history, followed by a decision regarding the most likely correct date of receipt. For example, in one case a DTP-HIB vaccine was shown as having been received 180 days prior to the birth of the child. By changing the date of

receipt by one year, the vaccine lined up with other vaccine receipts that occurred when the child was 185 days old.

3) Check for receipts of anything other than HepB during first 30 days of life.

Receipts of anything other than HepB or HepB immune globulin were treated as data entry errors. Examples include a record of a receipt of HIB at age 2-days, and for a different child, a receipt of DTP at age 1-day. In both cases the children received HepB vaccinations on those days. In both cases it was believed that the entries of the HIB and DTP vaccines were inadvertent.

4) Identify and check any histories indicating more than 3 HepB receipts in the first year of life.

The vaccine histories of children with more than three HepB receipts during the first year of life were examined by the study team. In instances where the receipts occurred around birth, 2 months, 4 months, and 6 to 12 months, the histories were deemed to be plausible and no further action was taken. When the four receipts deviated considerably from that pattern, staff from the relevant HMO went back to the child's medical charts to look for clues as to what might have happened. In one example, receipts were listed at birth, around 1 month, around 6 months, and around 7 months. Review of the charts indicated that the record of receipt near 7 months was an error. That receipt was omitted from the child's resolved vaccine history.

5) Identify and check any histories indicating more than 3 DT receipts (including DTPs, DTaPs, TT, experimental DTaP vaccines, DTaP-HIB or DTP-HIB combinations, etc) in the first year of life.

The vaccine histories of children with more than three DT receipts during the first year of life were examined by the study team. In instances where the receipts occurred around 2, 4, 6, and 12 months, the histories were deemed to be plausible and no further action was taken. When the four receipts deviated considerably from that pattern, staff from the relevant HMO went back to the child's medical charts to look for clues as to what might have happened. In one example, receipts were listed at days 66, 121, 154, and 188. Review of the charts indicated that the record of receipt at 154 days was an error. That receipt was omitted from the child's resolved vaccine history.

6) Identify and check any histories indicating more than 4 HIB receipts (including combination vaccines with DTP or DTaP) in the first year of life.

A finding that a child's vaccine history indicated more than 4 HIB receipts triggered a chart review by staff at the relevant HMO. In one case, the receipt of 5 HIBs by a single child within the first year of life was deemed to be accurate.

7) Identify and check any histories indicating a receipt of an influenza vaccine in the first 120 days of life.

It would be unusual to receive a flu shot in this age range. None were found.

8) Checks for Hepatitis-A, MMR, varicella and polio vaccines.

These vaccines never contained thimerosal, so obtaining clean histories was not critical for these vaccines. However, checks were run to help identify anomalies in the children's histories. Checks included identification of histories where either varicella or MMR vaccine was received in the first 180 days of life, histories where any hepatitis-A vaccine was received before age 1 year, and histories indicating more than three polio receipts in the first year

A list of all vaccine types remaining in the resolved vaccine histories of all children, and the amount and the mercury amount assigned to each receipt is shown in Section 7.2.4.

Exhibit 7.2.3.1
Example Vaccine History: Record of HepB Vaccine Receipt at Age 2-Days Shown in Chart Data, but no Corresponding Record in Computer-Automated Data.

	Resolved Vaccine History			Decision Rule Indicators							Chart, Computer-automated, and Parent Provided Immunization Data							
ID	Age Days	Res. Vac.	Res. Mfr.	HepB Polio R1	HepB Polio R2	DTP HIB R1	DTP HIB R2	Same Day Dup.	Bad Date	Look up	Age Days	Chart Vac.	Cmptr Vac.	Parent Vac.	Chart Mfr.	Cmptr Mfr.	Chart Lot	Cmptr Lot
258	2	HepB	MIS								2	HepB			MIS		MIS	
258	54	HepB	SKB								54	HepB	HepB		ENG	SKB	ENG	110
258	60	DTP	CON								60	DTP	DTP		CON	CON	2B4	2B4
258	60	HIB	PRX								60	HIB	HIB		PRA	PRX	M13	M13
258	60	Polio	LED								60	Polio	Polio		LED	LED	67	67
258	178	DTP	LED								178	DTP	DTP		LED	LED	350	350
258	178	HIB	PRX								178	HIB	HIB		PRA	PRX	M13	M13
258	178	Polio	LED								178	Polio	Polio		LED	LED	352	352
258	233	DTP	CON								233	DTP	DTP		CON	CON	3J4	3J4
258	233	HIB	PRX								233	HIB	HIB		PRA	PRX	M13	M13
258	233	Polio	LED								233	Polio	Polio		LED	LED	352	352
258	282	HepB	SKB								282	HepB	HepB		ENG	SKB	128	128
258											465	DTP	DTP		CON	CON	3F5	3F5
258											465	HIB	HIB		PRA	PRX	M71	M71
258											465	MMR	MMR		MSD	MSD	116	116

Notes: For brevity, manufacturer and lot numbers are truncated to three characters. Actual values span more characters and may include blank spaces. Resolved vaccine history includes only vaccines received in the age range of 1 to 365 days.

Exhibit 7.2.3.2
Example Vaccine History: Combined DTP-HIB Vaccines Retained on Days 121, and 185 While Separate DTP and HIBs Omitted from Same Days Because Former Had Manufacturer and Lot Number. Same-Day-Duplicate HIBs Omitted on Day 63.

	Resolved Vaccine History			Decision Rule Indicators							Chart, VSD, and Parent Provided Immumization Records Data							
ID	Age Days	Res. Vac.	Res. Mfr.	HepB Polio R1	HepB Polio R2	DTP HIB R1	DTP HIB R2	Same Day Dup.	Bad Date	Look up	Age Days	Chart Vac.	Cmptr Vac.	Parent Vac.	Chart Mfr.	Cmptr Mfr.	Chart Lot	Cmptr Lot
26	1	HepB	MIS								1	HepB	HepB		MIS	UNK	MIS	
26								1			63		HIB			MSD		136
26								1			63		HIB			UNK		
26	63	DTP	CON								63	DTP	DTP		MIS	CON	MIS	3D5
26	63	HIB	MSD								63	HIB	HIB		MIS	MSD	MIS	136
26	63	HepB	SKB								63	HepB	HepB		MIS	SKB	MIS	ENG
26	63	Polio	LED								63	Polio	Polio		MIS	LED	MIS	71
26	121	DTP-HIB	LED								121		DTP-HIB			LED		390
26						1					121	DTP	DTP		MIS	UNK	MIS	
26						1					121	HIB	HIB		MIS	UNK	MIS	
26	121	Polio	LED								121	Polio	Polio		MIS	LED	MIS	71
26	185	DTP-HIB	LED								185		DTP-HIB			LED		390
26						1					185	DTP	DTP		MIS	UNK	MIS	
26						1					185	HIB	HIB		MIS	UNK	MIS	
26	185	HepB	SKB								185	HepB	HepB		MIS	SKB	MIS	ENG
26	185	Polio	LED								185	Polio	Polio		MIS	LED	MIS	71
26											371		DTP-HIB			UNK		
26											371		MMR			UNK		
26											371	DTP	DTP		MIS	UNK	MIS	
26											371	HIB	HIB		MIS	UNK	MIS	

Notes: For brevity, manufacturer and lot numbers are truncated to three characters. Actual values span more characters and may include blank spaces.
Resolved vaccine history includes only vaccines received in the age range of 1 to 365 days.

Exhibit 7.2.3.3
Example Vaccine History: Day 117 HIB and Polio Vaccines Omitted from Resolved History Because Same Vaccines on Day 120 Have Matching Parent Provided Data. DTaPs on Days 62, 120, and 174 Omitted Because DTPs on Same Days Have Manufacturer and Lot Numbers.

	Resolved Vaccine History			Decision Rule Indicators							Chart, VSD, and Parent Provided Immunization Records Data							
ID	Age Days	Res. Vac.	Res. Mfr.	HepB Polio R1	HepB Polio R2	DTP HIB R1	DTP HIB R2	Same Day Dup.	Bad Date	Look up	Age Days	Chart Vac.	Cmptr Vac.	Parent Vac.	Chart Mfr.	Cmptr Mfr.	Chart Lot	Cmptr Lot
373	1	HepB	MIS								1	HepB	HepB	HepB	MIS		MIS	
373						1					62			DTaP				
373	62	DTP	CON								62	DTP	DTP		CON	CON	400	400
373	62	HIB	PRX								62	HIB	HIB	HIB	PRA	PRX	M00	M00
373	62	HepB	SKB								62	HepB	HepB	HepB	SKE	SKB	ENG	173
373	62	Polio	LED								62	Polio	Polio	Polio	LED	LED	428	428
373							1				117		HIB			PRX		M00
373					1						117		Polio			LED		432
373						1					120			DTaP				
373	120	DTP	LED								120	DTP			LED		431	
373	120	HIB	PRA								120	HIB		HIB	PRA		M00	
373	120	Polio	LED								120	Polio		Polio	LED		432	
373						1					174			DTaP				
373	174	DTP	CON								174	DTP	DTP		CON	CON	M56	5M6
373	174	HIB	PRX								174	HIB	HIB	HIB	PRA	PRX	M23	M23
373	174	Polio	LED								174	Polio	Polio	Polio	LED	LED	430	430
373	306	HepB	SKB								306	HepB	HepB	HepB	SKB	SKB	ENG	ENG

Notes: For brevity, manufacturer and lot numbers are truncated to three characters. Actual values span more characters and may include blank spaces. Resolved vaccine history includes only vaccines received in the age range of 1 to 365 days.

Exhibit 7.2.3.4
Example Vaccine History: HIB and Polio Receipts from Day 130 Omitted, Same Vaccines Received on Day 131 Retained. Choice of Which to Omit and Which to Retain was Random.

	Resolved Vaccine History			Decision Rule Indicators							Chart, VSD, and Parent Provided Immunization Records Data							
ID	Age Days	Res. Vac.	Res. Mfr.	HepB Polio R1	HepB Polio R2	DTP HIB R1	DTP HIB R2	Same Day Dup.	Bad Date	Look up	Age Days	Chart Vac.	Cmptr Vac.	Parent Vac.	Chart Mfr.	Cmptr Mfr.	Chart Lot	Cmptr Lot
300	11	HepB	SKB								11	HepB			SKB		139	
300	60	HIB	PRX								60	HIB	HIB		PRA	PRX	M17	M17
300	60	HepB	SKB								60	HepB	HepB		SKB	SKB	ENG	ENG
300	60	Polio	PMC								60	Polio	Polio		PAS	PMC	J06	JO6
300							1				130	HIB			PRA		M28	
300					1						130	Polio			PAS		J11	
300	131	HIB	PRX								131		HIB			PRX		M28
300	131	Polio	PMC								131		Polio			PMC		J11
300	183	HIB	PRX								183	HIB	HIB		PRA	PRX	M28	M28
300	183	Polio	PMC								183	Polio	Polio		CON	PMC	J11	J11

Notes: For brevity, manufacturer and lot numbers are truncated to three characters. Actual values span more characters and include may blank spaces.
Resolved vaccine history includes only vaccines received in the age range of 1 to 365 days.

7.2.4. Mercury Amount Assigned to Each Childhood Vaccine or Immune Globulin Receipt

Each vaccine or immune globulin listed in each child's resolved vaccine history was assigned a mercury amount. Our reference sources for determining the amount of mercury contained in each receipt included the 1995 and 2000 Physician's Desk References (PDRs), Pediatrics (1999), Plotkin & Orenstein (1999), Plotkin & Mortimer (1994), the Food and Drug Administration (FDA) website (accessed on 2/28/2003), and personal communication with vaccine experts at the FDA. The mercury amounts contained in experimental vaccines were provided by the participating HMOs, using data from their own records.

Exhibit 7.2.4.1 shows all of the vaccine types listed in the children's resolved vaccination histories, their frequency of occurrence, and the mercury amount assigned to each. For the time frame in which these vaccines were administered (all were received between 01/03/1993 and 01/08/1998), most of the vaccines had a single, constant mercury amount that did not vary by manufacturer. For example, all hepatitis-b vaccines available during that time contained 12.5 micrograms of ethylmercury per dose. Exceptions were DTaP, TD, pneumococcal, HIB vaccines, and experimental vaccines. Smithkline Beecham licensed a thimerosal-free DTaP vaccine under the name Infanrix on 1/29/1997. Prior to that all available DTaP vaccines contained 25 micrograms of ethylmercury per dose. The database of resolved vaccine histories include two receipts of Smithkline Beecham DTaPs after 1/29/1997, but both were so soon after the license date that we made the assumption that these two instances were not receipts thimerosal-free vaccine. We therefore assumed these two doses contained 25 micrograms of ethylmercury each. The receipt dates were 2/19/97, and 3/21/97.

Almost all of the tetanus/diphtheria (TD) in use during that time frame contained 25 micrograms of ethylmercury per dose. An exception was a TD vaccine manufactured by Massachusetts Biologic Laboratories, which contained only 8.3 micrograms per dose. However, the database contained no TD receipts where the manufacturer was Massachusetts Biologic Laboratories.

Lederle made two pneumococcal vaccines in that time frame, one of which contained 25 micrograms of ethylmercury (product name = Pnu-Imune 23), while the other contained zero micrograms of mercury (product name = Prevnar). The resolved vaccine histories do include pneumococcal receipts where the manufacturer was Lederle. We know, however, that at the one HMO where these pneumococcal receipts occurred, that the only product in use at the time was the Prevnar product. Therefore, all pneumococcal receipts from that HMO were assigned a mercury amount equal to zero micrograms. Children from other HMOs with pneumococcal receipts in their resolved vaccine histories were known or assumed[9] to have received the Merck product, which contained zero micrograms of ethylmercury.

[9] Of the 92 pneumococcal receipts in the resolved vaccine histories, only 1 receipt did not have any information on manufacturer. We assumed this receipt contained zero micrograms of ethylmercury.

HIB vaccines in use at that time contained zero, 12.5, or 25 micrograms of ethylmercury, depending on the type and manufacturer. The HIB PRP-T vaccines made by Connaught, Aventis Pasteur, Pasteur Merieux Connaught, and Smithkline Beecham with product names ActHIB and OmniHIB contained zero micrograms of ethylmercury per dose. The HIB PRP-OMP manufactured by Merck & Company with product name PedvaxHIB contained 12.5 micrograms of ethylmercury per dose. And HIB HbOC vaccine made by Lederle / Praxis with product name HibTITER contained 25 micrograms of ethylmercury per dose.

Exhibit 7.2.4.1
Vaccine Types in Resolved Vaccine Histories and Amount of Ethylmercury in Each Receipt

Vaccine Type	Mercury Amount (Micrograms)	Frequency	Comment
DT TD	25	23	Diphtheria and tetanus
DTP	25	1477	Diphtheria, tetanus, pertussis
DTP-HIB	25	1328	Combined DTP-HIB
DTaP	25	135	Diphtheria, tetanus andacellular pertussis
DTaP-HIB	25	4	Combined DTaP-HIB
DTaPHepB	12.5	6	Experimental combined DTaP-HepB
Flu	12.5	4	Influenza
HBIG	25	7	Hepatitis B immune globulin
HIB	0	47	H. influenzae type b MercAmt=0 if Connaught/Merieux/Pasteur PRP-T ActHIB, or SKB/GSK PRP-T OmniHIB
HIB	12.5	472	H. influenzae type b MercAmt=12.5 if MSD PedVax-HIB
HIB	25	983	H. influenzae type b MercAmt=25 if Lederle/Praxis/WAL HbOC Hibtiter.
HepA	0	5	Hepatitis A
HepB	12.5	2828	Hepatitis B
MMR	0	17	Measles, Mumps, Rubella
Pneumo	0	92	Pneumococcal
Polio	0	2740	Polio
TT	25	3	Tetanus toxoid
Varicel	0	3	Varicella
X01DTaP	0	9	X01 Experimental DTaP
X02(DTaP	25	9	X02 Experimental (Acelimune)
X03	25	3	X03 Experimental (Tetracel)
X03(D-H)	25	3	X03 Experimental (Tetracel)
X10	0	6	X10 Experimental Meningicoccal
		10204	

7.3. Measures of Prenatal Exposure to Ethylmercury

7.3.1. Introduction to the Prenatal Ethylmercury Exposures File

Two sources of prenatal vaccination data (maternal medical chart abstraction, and maternal interview) were combined to create a *Prenatal Ethylmercury Exposures File.* This file contains data on maternal exposure to ethylmercury from thimerosal-containing vaccines and immune globulins received by the mothers of study participants during their pregnancies with the focus children. The file contains one record per mother (n=1,047). Each record lists the types of vaccines and immune globulins received, the amounts of ethylmercury corresponding to each receipt, and the timing of each receipt. The timing of receipt is expressed as the number of months from the receipt to the birth of the focus child.

Examples of several prenatal records are shown in Exhibit 7.3.1.1. The first record (ID = "x1") corresponds to a mother who received a Gamulin injection (an immune globulin) 3.0 months prior to the birth of the focus child. The mercury amount corresponding to a Gamulin receipt was assigned as 50 micrograms of ethylmercury. The example in the second row (ID= "x2") is a mother who received a rhogam injection (an immune globulin) 2.8 months prior to the birth of the focus child. Rhogam is assumed to have contained 12.75 micrograms of ethylmercury per receipt[10]. ID "x3" received two immune globulin injections during her pregnancy, each containing 50 micrograms of ethylmercury, resulting in a total prenatal exposure amount equal to 100 micrograms.

ID "x4" received an immune globulin 2.6 months before the focus child was born, and received another on the day the child was born. Receipts on the day of the birth of the focus child were assumed to have occurred after delivery, and are therefore not counted in the total prenatal exposure amount. ID "x5" received adult dose influenza and tetatnus vaccines during her pregnancy, resulting a total exposure amount equal to 50 micrograms. ID "x6" received a hepatitis-B vaccination resulting in 12.5 micrograms of ethylmercury exposure. And, ID "x7" did not receive any vaccinations or immune globulins during her pregnancy with the focus child.

[10] Additional detail is provided in Section 7.3.3

Exhibit 7.3.1.1
Example Records of Prenatal Ethylmercury Exposures from Thimerosal-containing Vaccines and Immune Globulins

	Prenat-	Immune Globulin 1				Immune Globulin 2				Flu		HepB		Tetanus		DT	
ID	thimer	Type	Amt	Mos	Dose	Type	Amt	Mos	Dose	Amt	Mos	Amt	Mos	Amt	Mos	Amt	Mos
x1	50	GAMULIN	50	3.0	1CC												
x2	12.75	RHOGAM	12.75	2.8	SINGLE DOS												
x3	100	GAMULIN	50	5.3	UNK (FULL)	GAMULIN	50	2.5	UNK (FULL)								
x4	50	GAMULIN	50	2.6	J23003	GAMULIN	0	0	J24110								
x5	50									25	7.0			25	0.8		
x6	12.5											12.5	6.6				
x7	0																

PrenatThimer = total ethylmercury exposure from vaccines and immune globulins during pregnancy with focus child.
Columns labled "Amt" show the ethylmercury amount corresponding to a vaccine or immune globulin receipt.
Columns labeled "Mos" show the number of months between receipt and birth of the focus child.
"Flu" = influenza vaccine, "HepB" = hepatitis-B vaccine, "Tetanus" = tetanus, and "DT" = diphtheria-tetanus. Records indicated that these were the only types of thimerosal-containing vaccines received by the mothers of study participants during their pregnancies with the focus children.

7.3.2. Overview of Steps from Raw Data to Creation of Analysis Variables

Data on prenatal exposure to ethylmercury from thimerosal containing vaccines and immune globulins were obtained from two sources: From abstractions of maternal medical charts covering the period that the mother was pregnant with the focus child, and from questionnaire items from the parent interview. An overview of the data processing steps from the receipt of raw data files to the creation of the exposure variables used in analyses is as follows:

1. The master list of study IDs was merged to the maternal medical chart and parent interview files. Any problems with ID discrepancies were resolved at this stage. The master list of IDs, the maternal medical chart, and the parent interview data files each contained one record per child ID. The master list of study IDs contained each child's ID and date of birth. The maternal chart file contained a field for Rh-blood group status of the mother. It also contained fields for the date, dosage, manufacturer, and product names of immune globulins received, and for dates and types of vaccines received by the mother. The parent interview file contained data from questionnaire items that explained that women with Rh-negative blood types often receive rhogam or other immune globulins during pregnancy to prevent problems with blood incompatibility, and asked the mother if she had received any rhogam or other immune globulins during her pregnancy with the focus child.
2. For chart records, all entries indicating the type of immune globulin received were recoded to correct spelling errors and variations in abbreviations. For example, an incorrectly spelled entry indicating receipt of "rhogan" would have been recoded to take the value "RHOGAM".

3. Next, we calculated the number of months between vaccine or immune globulin receipt and the date of delivery. Only those receipts that occurred within the period spanning ten months (256 days) prior to the delivery date were counted towards the total amount of prenatal exposure to ethylmercury from thimerosal. Immune globulins received on the day of delivery were assumed to have occurred after delivery, and were therefore not counted in the calculation of prenatal exposure.
4. In the next step, discrepancies between the maternal medical chart-abstracted data and the parent interview data on receipt of immune globulins during pregnancy were resolved. During the weekly conference calls, the entire study team reviewed all available data for discrepant cases. If the mother was rh-negative, and either of the two data sources indicated receipt of an immune globulin during pregnancy, then it was assumed that a receipt had occurred. Additional details on this step are provided in Section 7.3.4 of this document.
5. A mercury exposure amount was assigned to each vaccine or immune globulin receipt. See Section 7.3.5 for details.
6. Finally, a measure of total ethylmercury exposure from vaccine and immune globulins received during pregnancy was created. For example, a child whose mother received two vaccines during her pregnancy that each contained 25 micrograms of ethylmercury, e.g., a flu shot and a tetanus shot, would have a received a value of 50 micrograms on this measure. This measure was used in the analytical models and was defined as follows:
    - *PrenatThimer* = "Prenatal exposure to ethylmercury from thimerosal" = The sum total of mercury amounts from all thimerosal containing vaccines and immune globulins received by the mother during her pregnancy with the focus child.

7.3.3. Cleaning of Prenatal Ethylmercury Exposures Data

The chart-abstracted data on vaccine receipts during pregnancy were straightforward. The records listed the types of and dates of vaccine receipts. Using the date of vaccine receipt and the child's date of birth, we calculated the number of months from receipt to birth and assigned an exposure amount to the vaccine receipt only if the receipt occurred before the child was born, and less than 10 months prior to the birth of the child. Although the rule we applied would have counted receipts 10 months prior to birth (to account for the possibility of late births) there were no receipts listed in the data set that were near 10 months. In these data we found one occurrence of a diphtheria-tetanus (DT) receipt that was 9.2 months prior to the birth of the child. All other vaccine receipts that were counted toward the total exposure amounts were less than 9 months prior to birth.

The chart-abstracted data included records of receipts of the following thimerosal-containing vaccines: Influenza, tetanaus, diphtheria-tetanus, and hepatitis-B. There were also records of rubella vaccine receipts, but the rubella vaccines did not contain thimerosal and were therefore of no consequence to the analyses.

The data on immune globulin receipts were less straightforward for several reasons. The first was that the information on the product name and manufacturer sometimes

conflicted with one another, or was sometimes missing entirely. This was a problem because the amount of mercury included in a dose varied according to the product received. A second potential conflict was between the mother's recorded rh-status and immune globulin receipt. The expectation is that rh-positive mothers would not receive immune globulins and rh-negative mothers would usually receive immune globulins, although this was not always the case. Finally, there was the potential for discrepancy between the mother's recollection of immune globulin receipt, as reported in the parent interview, and the data recorded in the medical charts. The resolutions for each of these types of discrepancies are described below.

An example of a discrepancy between a product name (type) and the product manufacturer is a record that indicates that the product received was Rhogam and the manufacturer was Armour. The product made by Armour was called Gamulin, and thimerosal content in Gamulin was different than that of Rhogam. This discrepancy probably occurred because, even though Rhogam is a specific product, the name "rhogam" is often used as a generic term similar to the way "kleenex" is often used a generic term to refer to facial tissues, even though Kleenex is a specific product. Therefore, whenever a manufacturer or lot number was listed in the record that pointed toward the receipt of a specific product, that information took precedence over the information listed in the product type field. The Prenatal Ethylmercury Exposures File includes the original text for product type and manufacturer, as well as the resolved product type. The resolved product type represents our best estimate of what was actually received, and was used for the purpose of assigning a mercury exposure amount.

Rhogam was the most commonly listed type of immune globulin at all four HMOs. In cases where the evidence pointed to the receipt of an immune globulin, but where there was no information on product type, manufacturer, or lot number, we assumed the receipt was Rhogam. Section 7.3.4 describes variables that were created and analyses that were conducted to evaluate the sensitivity of the model results to this assumption.

For each record we had to make a judgment, based on the available evidence, as to whether the mother received an immune globulin during her pregnancy with the focus child, and if so, what type of immune globulin was received. A set of codes was developed to document the decisions that were made. The codes are shown in the column labeled "Decision code" of Exhibit 7.3.3.1 and are defined as follows:

- Decision code 1 = prenatal immune globulin received: The chart indicated that the mother was rh-negative, the mother reported having received an immune globulin during her pregnancy with the focus child, and the chart abstraction listed an immune globulin receipt within the period spanning ten months prior to the birth of the child.

- Decision code 2 = prenatal immune globulin received: Although the mother did not know whether she had received an immune globulin during her pregnancy with the focus child, the chart clearly indicated that the mother was rh-negative,

and the chart abstraction listed an immune globulin receipt within the period spanning ten months prior to the birth of the child.

- Decision code 3 = prenatal immune globulin received: For these records there was a discrepancy between the mother report and the chart-abstracted data. Although the mother reported that she did not receive an immune globulin during her pregnancy with the focus child, the chart clearly indicated that the mother was rh-negative, and the chart abstraction listed an immune globulin receipt within the period spanning ten months prior to the birth of the child. We assumed the mothers' memories were in error and the chart data were correct.

- Decision code 4 = prenatal immune globulin received: The mother and the chart agreed that there had been an immune globulin receipt, but the type of immune globulin was not recorded in the records. Receipt of Rhogam was assumed.

- Decision code 5 = prenatal immune globulin received: The mother indicated that she had received a prenatal immune globulin. According to the chart abstracted data, these mothers were either rh-negative or their rh-status was not recorded. The types and dates of receipts were not recorded. For these records we assumed the mother report was correct and assumed Rhogam receipts were prior to the birth of the child.

- Decision code 6 = prenatal immune globulin received: For this record, we assumed that the chart data indicating that the mother was rh-positive was an error, and assumed the remaining data from both the mother report and the chart were correct. The mother and the chart agreed that there had been an immune globulin receipt, and the chart indicated the type and date of receipt.

- Decision code 7 = no prenatal immune globulin received: For each of these records, the mother indicated that she had received a prenatal immune globulin, but the chart indicated that she was rh-positive and that no receipts had occurred. We assumed the mother's recollection was in error and that the chart was accurate.

- Decision code 8 = no prenatal immune globulin received: The charts indicated that the mother was rh-positive and contained no indication of immune globulin receipt. The mothers in this group either said 'no' or they did not know whether they had received and immune globulin during their pregnancies with the focus children.

- Decision code 9 = no prenatal immune globulin received: For each of these records, both the mother and the chart indicated receipts of immune globulins, but the chart showed that the receipts occurred after the birth of the child. Note that receipts that occurred on the day of the child's birth (indicated as *Months Prior to Birth* =0 in Exhibit 7.3.3.1) were assumed to have occurred after delivery and were not counted as prenatal exposures.

- Decision code 10 = no prenatal immune globulin received: Although the chart indicated that the mother was rh-negative, a check-box on the chart abstraction form indicated that no immune globulins had been received. The mother also reported that she had not received an immune globulin during her pregnancy with the focus child.

- Decision code 11 = no prenatal immune globulin received: The mothers in this group indicated that they had not received an immune globulin during their pregnancies with the focus children. The chart data fields were mostly missing or incomplete. The assumption of no prenatal immune globulin receipts was based primarily on the maternal report.

- Decision code 12 = no prenatal immune globulin received: Notes written on the chart indicated that no immune globulins were needed. In one case the mother's husband was rh-negative, in the other case there was no note about the father rh-status but the child was rh-negative so there was no issue of incompatibility.

Exhibit 7.3.3.1
Data Cleaning Decision Codes for Prenatal Immune Globulin Receipts

Decision Code	Chart Rh Status	Mother Reported IG Receipt	Original Chart Text for IG Receipt	Cleaned Text for IG Receipt	Assigned Mercury Amount	Months Prior to Birth	Chart Check Box IG Received	Freq.
1	RhNeg	Yes	GAMULIN	GAMULIN	50	2.83	Yes	1
1	RhNeg	Yes	GAMULIN	GAMULIN	50	3.03	Yes	1
1	RhNeg	Yes	HYP RHO-D	HYPRHO-D	50	1.61	Yes	1
1	RhNeg	Yes	HYPRHO-D	HYPRHO-D	50	2.47	Yes	1
1	RhNeg	Yes	J24211	GAMULIN	50	2.66	Yes	1
1	RhNeg	Yes	MISSING	RHOGAM	12.75	2.14	Yes	1
1	RhNeg	Yes	MISSING	RHOGAM	12.75	2.57	Yes	1
1	RhNeg	Yes	MISSING	RHOGAM	12.75	2.93	Yes	1
1	RhNeg	Yes	MISSING	RHOGAM	12.75	2.96	Yes	1
1	RhNeg	Yes	MISSING	RHOGAM	12.75	3.09	Yes	1
1	RhNeg	Yes	MISSING	RHOGAM	12.75	5.56	Yes	1
1	RhNeg	Yes	RHL174	RHOGAM	12.75	2.89	Yes	1
1	RhNeg	Yes	RHL228	RHOGAM	12.75	5.72	Yes	1
1	RhNeg	Yes	RHO GAM	RHOGAM	12.75	2.3	Yes	1
1	RhNeg	Yes	RHOD	HYPRHO-D	50	2.57	Yes	1
1	RhNeg	Yes	RHOGAM	GAMULIN	50	2.11	Yes	1
1	RhNeg	Yes	RHOGAM	GAMULIN	50	2.6	Yes	1
1	RhNeg	Yes	RHOGAM	GAMULIN	50	5.33	Yes	1
1	RhNeg	Yes	RHOGAM	RHOGAM	12.75	1.71	Yes	1
1	RhNeg	Yes	RHOGAM	RHOGAM	12.75	1.74	Yes	1
1	RhNeg	Yes	RHOGAM	RHOGAM	12.75	1.84	Yes	1
1	RhNeg	Yes	RHOGAM	RHOGAM	12.75	1.97	Yes	1
1	RhNeg	Yes	RHOGAM	RHOGAM	12.75	2.04	Yes	1
1	RhNeg	Yes	RHOGAM	RHOGAM	12.75	2.14	Yes	1

Exhibit 7.3.3.1
Data Cleaning Decision Codes for Prenatal Immune Globulin Receipts

Decision Code	Chart Rh Status	Mother Reported IG Receipt	Original Chart Text for IG Receipt	Cleaned Text for IG Receipt	Assigned Mercury Amount	Months Prior to Birth	Chart Check Box IG Received	Freq.
1	RhNeg	Yes	RHOGAM	RHOGAM	12.75	2.17	Yes	2
1	RhNeg	Yes	RHOGAM	RHOGAM	12.75	2.24	Yes	2
1	RhNeg	Yes	RHOGAM	RHOGAM	12.75	2.34	Yes	1
1	RhNeg	Yes	RHOGAM	RHOGAM	12.75	2.4	Yes	1
1	RhNeg	Yes	RHOGAM	RHOGAM	12.75	2.57	Yes	1
1	RhNeg	Yes	RHOGAM	RHOGAM	12.75	2.76	Yes	4
1	RhNeg	Yes	RHOGAM	RHOGAM	12.75	2.8	Yes	3
1	RhNeg	Yes	RHOGAM	RHOGAM	12.75	2.89	Yes	4
1	RhNeg	Yes	RHOGAM	RHOGAM	12.75	3.03	Yes	1
1	RhNeg	Yes	RHOGAM	RHOGAM	12.75	3.06	Yes	1
1	RhNeg	Yes	RHOGAM	RHOGAM	12.75	3.09	Yes	2
1	RhNeg	Yes	RHOGAM	RHOGAM	12.75	3.26	Yes	1
1	RhNeg	Yes	RHOGAM	RHOGAM	12.75	3.29	Yes	1
1	RhNeg	Yes	RHOGAM	RHOGAM	12.75	3.42	Yes	1
1	RhNeg	Yes	RHOGAM	RHOGAM	12.75	3.45	Yes	1
1	RhNeg	Yes	RHOGAM	RHOGAM	12.75	3.55	Yes	2
1	RhNeg	Yes	RHOGAM	RHOGAM	12.75	4.87	Yes	1
1	RhNeg	Yes	RHOGAM	RHOGAM	12.75	5.3	Yes	1
1	RhNeg	Yes	RHOGAM	RHOGAM	12.75	5.69	Yes	1
1	RhNeg	Yes	RHOGAM	RHOGAM	12.75	5.72	Yes	1
1	RhNeg	Yes	RHOGAM	RHOGAM	12.75	6.74	Yes	1
1	RhNeg	Yes	RHOGAN	RHOGAM	12.75	4.47	Yes	1
1	RhNeg	Yes	Rhogam	RHOGAM	12.75	2.5	Yes	1
1	RhNeg	Yes	Rhogam	RHOGAM	12.75	2.83	Yes	1
1	RhNeg	Yes	Rhogam	RHOGAM	12.75	3.03	Yes	1
1	RhNeg	Yes	UNK	RHOGAM	12.75	2.8	Yes	1
2	RhNeg	DK	MISSING	RHOGAM	12.75	2.04	Yes	1
2	RhNeg	DK	RHOGAM	RHOGAM	12.75	1.22	Yes	1
2	RhNeg	DK	RHOGAM	RHOGAM	12.75	2.93	Yes	1
2	RhNeg	DK	UNK	RHOGAM	12.75	2.76	Yes	1
3	RhNeg	No	MICROHOGAM	MICRHOGAM	11.25	5.66	Yes	1
3	RhNeg	No	MISSING	RHOGAM	12.75	3.16	Yes	1
3	RhNeg	No	MISSING	RHOGAM	12.75	5.39	Yes	1
3	RhNeg	No	MISSING	RHOGAM	12.75	6.61	Yes	1
3	RhNeg	No	RHOGAM	GAMULIN	50	5	Yes	1
3	RhNeg	No	RHOGAM	RHOGAM	12.75	2.01	Yes	1
3	RhNeg	No	RHOGAM	RHOGAM	12.75	2.53	Yes	1
3	RhNeg	No	RHOGAM	RHOGAM	12.75	2.73	Yes	1
3	RhNeg	No	RHOGAM	RHOGAM	12.75	3.22	Yes	1
4	RhNeg	Yes		RHOGAM	12.75	2.34	Yes	1
4	RhNeg	Yes		RHOGAM	12.75	3.03	Yes	1
4	RhNeg	Yes		RHOGAM	12.75	5.26	Yes	1

Exhibit 7.3.3.1
Data Cleaning Decision Codes for Prenatal Immune Globulin Receipts

Decision Code	Chart Rh Status	Mother Reported IG Receipt	Original Chart Text for IG Receipt	Cleaned Text for IG Receipt	Assigned Mercury Amount	Months Prior to Birth	Chart Check Box IG Received	Freq.
4	RhNeg	Yes		RHOGAM	12.75	7.3	Yes	1
4	RhNeg	Yes		RHOGAM	12.75	7.83		1
5	RhNeg	Yes		RHOGAM	12.75	3		1
5	Unk	Yes		RHOGAM	12.75	3		6
6	RhPos	Yes	RHOGAM	GAMULIN	50	2.66	Yes	1
7	RhPos	Yes			.	.	No	2
8	RhPos	DK			.	.		1
8	RhPos	DK			.	.	No	13
8	RhPos	No			.	.		113
8	RhPos	No			.	.	No	748
9	RhNeg	Yes			.	-21.18	Yes	1
9	RhNeg	Yes	MISSING		.	-0.03	Yes	1
9	RhNeg	Yes	RHIMGLOB		.	0	Yes	1
9	RhNeg	Yes	RHL241A		.	-0.03	Yes	1
9	RhNeg	Yes	RHOGAM		.	0	Yes	1
9	RhNeg	Yes	Rhogam		.	-0.03	No	1
9	RhNeg	Yes	UNKNOWN		.	0	Yes	1
10	RhNeg	No			.	.	No	7
11	Unk	No			.	.		64
11	Unk	No			.	.	No	2
12	RhNeg	Yes			.	.	No	2
							Total:	1047

7.3.4. Mercury Amount Assigned to Each Prenatal Vaccine or Immune Globulin Receipt

Similar to the process described for childhood vaccine receipts, each vaccine or immune globulin received by the mother during the prenatal period was assigned a mercury amount. Our reference sources for determining the amount of mercury contained in each vaccine receipt included the 1995 and 2000 Physician's Desk References (PDRs), Pediatrics (1999), Plotkin & Orenstein (1999), Plotkin & Mortimer (1994), the Food and Drug Administration (FDA) website (accessed on 2/28/2003).

Final determination of the amounts of ethylmercury in prenatal immune globulins were made in consultation with experts at the FDA and with the manufacturers of immune globulin products. The amounts assigned were as follows:

- Rhogam: Between 1993 and 1997 the fill volumes ranged from 0.5 to 1.2 milliliters (*ml*), with an assumed average fill volume of 0.85 ml. Thimerosal was present in Rhogam at 0.003% w/v, which is equivalent to 30 micrograms (μg) per *ml*. Thimerosal was 50 percent ethylmercury by weight. Multiplying the three quantities gives $30\frac{\mu g}{ml} \times 0.85ml \times 0.50 = 12.75\mu g$ of ethylmercury per receipt.

- MicRhogam: Between 1993 and 1997 the fill volumes ranged from 0.3 to 1.2 milliliters (*ml*), with an assumed average fill volume of 0.75 ml. Thimerosal was present in MicRhogam at 0.003% w/v, which is equivalent to 30 μg per *ml*. Thimerosal was 50 percent ethylmercury by weight. Multiplying the three quantities gives $30\frac{\mu g}{ml} \times 0.75ml \times 0.50 = 11.25\mu g$ of ethylmercury per receipt.

- Gamulin and Hyprho-d: The average fill volumes for Gamulin and Hyprho-d used between 1993 and 1997 are assumed to be 1.0 ml. Thimerosal was present in each type at 0.01% w/v, which is equivalent to 100 micrograms μg per *ml*. Thimerosal was 50 percent ethylmercury by weight. Multiplying the three quantities gives $100\frac{\mu g}{ml} \times 1.0ml \times 0.50 = 50\mu g$ of ethylmercury per receipt.

Exhibit 7.3.4.1 lists all of the thimerosal-containing vaccines and immune globulins received by the mothers during their pregnancies with the focus children. The exhibit also shows the amount of ethylmercury assigned to each receipt.

As described previously, the word "rhogam" is often used as a generic term even though it is a specific product. Since lot numbers and manufacturers were infrequently listed in the medical charts, there are many instances where the product type was listed as "rhogam", but where we are uncertain whether the term was being used generically or

was referring to the specific product “Rhogam”. If the term was being used generically, then we may have assigned the wrong mercury amount to the receipt. For example, if a Gamulin was administered, but the administering physician wrote in the chart that “rhogam” was given, then we would have mistakenly assigned the receipt a mercury amount equal to 12.75, instead of 50. The data set includes two variables, corresponding to IG receipts 1 and 2, that each reflect the level of uncertainty regarding the type of immune globulin received. Recall that up to two immune globulins were listed in the chart abstracted data.

For receipt number 1, we defined a variable named *PN_ProductInfo1* that could take the values “1” or “0”. A value of “1” reflects a high level of confidence that we have correct information on the type of product that was administered. The variable took the value “1” if the lot number or the manufacturer, or a product other than “rhogam” was recorded in the chart. These pieces of information provided specifics about the product that was received. Immune globulin receipts where *PN_ProductInfo1* takes the value “0” are those where we lack the specific information on the product received. In several cases we assumed that rhogam was received because we had no information on product type, and in the remaining cases the chart listed the type as “rhogam”, but we are unsure of whether the term “rhogam” was being used generically or was a reference to the specific product. For receipt number 2, the same type of variable was created and named *PN_ProductInfo2*.

We used the variables *PN_ProductInfo1* and *PN_ProductInfo2* in the following way. Our primary set of analyses utilized the prenatal mercury amounts listed in Exhibit 7.3.4.1. This is equivalent to an assumption that all receipts with low levels of certainty about the product types were Rhogam receipts, and hence contained 12.75 micrograms of ethylmercury. To evaluate the sensitivity of the model results to the potential misspecification of the type of immune globulin received (and hence the total prenatal mercury exposure amount) we fit an alternate set of models where we made an alternative assumption that all receipts with low levels of certainty about the product types, were Gamulin or Hyprho-d receipts, with 50 micrograms of ethylmercury. In these alternative models, if *PN_ProductInfo1* or *PN_ProductInfo2* was equal to zero, than mercury amount for the corresponding immune globulin receipt was set to 50 micrograms.

Exhibit 7.3.4.2 shows a three-way cross-tabulation of the variable *PN_ProductInfo1* with the variable containing the primary mercury amount assignments for immune globulin receipt number one (*PN_IG1_Amt*), and with the variable containing the alternate mercury amount assignments for immune globulin receipt number one (*PN_IG1_Amt_Alt*). The exhibit shows that there were 75 immune globulin receipts where the value of *PN_ProductInfo1* was 0 and the primary mercury amount was assigned as 12.75 micrograms. The alternate value for these 75 receipts was set to 50 micrograms. The same type of cross-tabulation for variables corresponding to immune globulin receipt number two are shown in Exhibit 7.3.4.3. Finally, Exhibit 7.3.4.4 shows a cross-tabulation of the primary variable measuring total prenatal mercury exposure from thimerosal (*PreNatThimer*), with the variable measuring total exposure calculated using the alternate amounts (*PreNatThimer_Alt*).

Exhibit 7.3.4.1
Thimerosal-containing Prenatal Vaccines and Immune Globulins and Amount of Ethylmercury in Each Receipt

Vaccine or Immune Globulin Type	Mercury Amount (Micrograms)	Freq.	Comment
Rhogam	12.75	88	Immune globulin
Micrhogam	11.25	1	Immune globulin
Gamulin	50	11	Immune globulin
Hyprho-d	50	3	Immune globulin
Influenza	25	9	Influenza (Adult Dose)
Tetanus	25	3	Tetanus
DT	25	8	Diphtheria-tetanus
HepB	12.5	1	Hepatitis – B

Exhibit 7.3.4.2
Cross-tabulation of PN_ProductInfo1, PN_IG1_Amt, and PN_IG1_Amt_Alt Variables

PN_ProductInfo1	PN_IG1_Amt	PN_IG1_Amt_Alt	Frequency	Cumulative Frequency
.	.	.	959	959
0	12.75	50	74	1033
1	11.25	11.25	1	1034
1	12.75	12.75	2	1036
1	50	50	11	1047

Exhibit 7.3.4.3
Cross-tabulation of PN_ProductInfo2, PN_IG2_Amt, and PN_IG_Amt_Alt Variables

PN_ProductInfo2	PN_IG2_Amt	PN_IG2_Amt_Alt	Frequency	Cumulative Frequency
.	.	.	1032	1032
0	12.75	50	11	1042
1	12.75	12.75	2	1044
1	50	50	3	1047

Exhibit 7.3.4.4
Cross-tabulation of PreNatThimer and PreNatThimer_Alt Variables

PreNatThimer	PreNatThimer_Alt	Frequency	Cumulative Frequency
0	0	936	936
11.25	11.25	1	937
12.5	12.5	1	938
12.75	12.75	4	942
12.75	50	65	1007
25	25	18	1025
25.5	100	9	1034
50	50	10	1044
62.75	100	1	1045
100	100	2	1047

7.4. Covariates

Exhibit 7.4.1 summarizes the data sources and construction of all variable that were used as covariates in the analytic models.

Exhibit 7.4.1 Data Sources and Construction of Variables Used as Covariates in Analytical Models

Variable	Description	Data Sources			Additional Details
		Parent Interview	Medical Abstract	Computer Automated	
Variables Included in Every Model					
ChildAge	Child Age (Yrs) at assessment	X	X		
sexmale	Sex of child 0=female, 1=male	X		X	
Birth weight	1 = if birth weight 2500-2999 grams 2 = Birth weight 3000-3999 grams 3 = Birth weight 4000+ grams		X	X	
Maternal IQ	1= Score in lower third of distribution 2= Score in middle third of distribution 3= Score in upper third of distribution				The Kaufman Brief Intelligence test
HOME_TotalIndex	"HOME" Total Index	X			Home Observation for Measurement of the Environment was administered as part of the parent interview. It is a measure of a child's home environment based on maternal self-report and interviewer observations. The total score is a sum of two subscores, a cognitive stimulation and an emotional support score. The total score has a wide variety of inputs that measure the quality of the home environment including family interaction patterns, physical attributes of the home, and intellectual attributes.

PctPoverty1	(Percent of poverty line)/100	X			Percent of poverty line calculated from household size, household income, and the 2004 poverty guidelines for the48 contiguous states and the District of Columbia shown in Department of Health and Human Services Annual Update of the HHS Poverty Guidelines; Federal Register, Vol. 69, No. 30, February 13, 2004 / Notices according to the following algorithm:
					if HH size=2 then Pov=HH Income/12490;
					if HH size=3 then Pov=HH Income/15670;
					if HH size=4 then Pov=HH Income/18850;

Exhibit 7.4.1 Data Sources and Construction of Variables Used as Covariates in Analytical Models

Variable	Description	Data Sources			Additional Details
		Parent Interview	Medical Abstract	Computer Automated	

					if HH size=5 then Pov=HH Income/22030;
					if HH size=6 then Pov=HH Income/25210;
					if HH size=7 then Pov=HH Income/28390;
					if HH size=8 then Pov=HH Income/31570;
					if HH size=9 then Pov=HH Income/(31570+3180);
					if HH size=10 then Pov=HH Income/(31570+6360);

Maternal Education	0= No HS degree 1=High school diploma or GED 2=attended some college, but no degree 3=Associate's degree or higher	X			
SingleParent	Child lives in a single parent household(0/1)	X			
Site	HMO-A HMO-B HMO-C HMO-D				Variable defines four categories of HMO sites where assessments took place.
Child and Family Characteristics					
Computer Experience	Child's experience with using computers	X			0=No experience, 1=some experience, 2=much experience.
Maternal Age	1= Maternal Age at Ch Birth: <=16 years 2=Maternal Age at Ch Birth: 17-39 years 3=Maternal Age at Ch Birth: >=40 years	X	X	X	
OlderSibs	Child has an older sibling (0/1)	X			=1 if child has older sibling living in home
YoungerSibs	Child has a younger sibling (0/1)	X			=1 if child has younger sibling living in home
DayCareCentr	# of center-based day care settings prior to KG	X			Number of center-based daycare settings attended by child prior to kindergarten.

Exhibit 7.4.1 Data Sources and Construction of Variables Used as Covariates in Analytical Models

		Data Sources			
Variable	**Description**	**Parent Interview**	**Medical Abstract**	**Computer Automated**	**Additional Details**
DayCareHome	# of home-based day care settings prior to KG	X			Number of home-based daycare settings attended by child prior to kindergarten.
EngOnly	English only at home	X			Binary indicator of whether English was the only language spoken in the child's home
Breast Feeding (Duration)	0 = Breast Fed: <1mo 1 =Breast Fed: 1-6mos 2 = Breast Fed: 6+ mos	X			
Child Birth Conditions					
cMedicalHist_1	=1 if IUGR or birth headCM +/- 2SD from Mean		X		A binary indicator of whether intrauterine growth retardation was diagnosed at birth or head circumference was +/- 2 standard deviations from national mean at birth. National means and standard deviations for head circumference measurements of U.S. boys and girls at birth obtained from Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC growth charts for the United States: Methods and development. National Center for Health Statistics. Vital Health Stat 11(246). 2002
C5APGARImpVal1	5-minute apgar		X		Child's score on the 5 minute APGAR, which is a test given to newborns five minutes after birth to measure activity, pulse, grimace, appearance, and respiration.
Prenatal Exposures (non-vaccine related)					
PreNatNicotine_1	Used tobacco during pregnancy	X	X		= 1 if mother used any tobacco products during pregnancy.
PreNatAlcohol_1	Alcohol use during pregnancy:	X	X		0= none 1= occasional (1-4 drinks per month) 2= light (20-24 drinks/month or 5-6 per week) 3=moderat e(10-15 drinks per week) 4=heavy (more than 15 drinks per week)
Tuna Consumption	Maternal tuna consumption during	X			0= no consumption of tuna during pregnancy.

Exhibit 7.4.1 Data Sources and Construction of Variables Used as Covariates in Analytical Models

Variable	Description	Data Sources			Additional Details
		Parent Interview	Medical Abstract	Computer Automated	
	pregnancy				1 = moderate consumption (less than one serving per week) 2 = high consumption (more than one serving per week)
PreNatFish_1	High consumption of fish during pregnancy.	X			1= if mother reported eating tuna, and ocean fish, and home-caught fish during pregnancy. 0 = else.
PreNatOrgMerc_1	Use of mercury-containing contact lens solutions or nasal sprays during pregnancy.	X			PreNatOrgMerc calculated as sum of PreNatContacts and PreNatNasal, defined below: PreNatContacts Use of thimerosal-containing contact lens solution during pregancy 2=high (regular use of this agent) 1=moderate (any non- regular use of this agent) 0=no use of this agent PreNatNasal Use of thimerosal-containing nasal sprays during pregancy 2=high (regular use of this agent) 1=moderate (any non- regular use of this agent) 0=no use of this agent
PreNatHomePro_1	Prenatal exposure to mercury from home products	X			=1 if any exposure to mercury during pregnancy from thermometers, florescent light bulbs, shoes, or switches; =0 else.
Tooth Amalgams	Mercury-containing dental amalgams	X			Amalgam fillings during pregnancy: 0 = mother had no amalgam fillings 1 = had amalgam filling, but no dental work and did not chew gum during pregnancy 2= had amalgam fillings and had dental work or chewed gum during pregnancy.
PreNatlead_1	Prenatal exposure to lead from occupational or residential sources	X			=1 if during pregnancy mother worked in:

Exhibit 7.4.1 Data Sources and Construction of Variables Used as Covariates in Analytical Models

Variable	Description	Data Sources			Additional Details
		Parent Interview	Medical Abstract	Computer Automated	
					Worked in smelting, soldering, construction, or demolition or if during pregnancy mother lived in : a pre-1950 home, or a pre-1978 home that underwent painting or renovation during her pregnancy.
PreNatIllDrug	1=Cocaine or Narcotic	X	X		1= if mother reported any use of cocaine, crack, heroin, methamphetamines, or speed during pregnancy, or maternal medical chart indicated suspected use or suspected use of cocaine or narcotics during pregnancy. 0 = else.
Child Medical Conditions					
IronDef_1	Anemia or iron deficiency		X		=1 if any records of anemia and iron deficiency in child's chart. =0 else.
ADHDstimulant	Use of ADHD stimulant in 12 hours prior to assessment	X	X	X	=1 if child used any of the following stimulant medications in the 12 hours prior to the clinical assessment: Focalin; Ritalin; Methylin; Ritalin SR; Methylin ER; Metadate ER; Ritalin LA; Metadate CD; Concerta; Desoxyn; Dextroamphetamine tablets (generic); DextroStat tablets; Dexedrine tablets; Adderall tablets; Dexedrine Spansules; Adderall XR capsules.
ChdPICA_1	Child Pica	X	X		= 1 if child has pica, which is characterized by persistent and compulsive cravings (lasting one month or longer) to eat nonfood items. =0 else.
Maternal Diagnoses					
MatLangDel	Maternal Language Delay	X	X		=1 if mother ever diagnosed as having language delay; =0 else.
MatSpeechDel	Maternal speech delay	X	X		=1 if mother ever diagnosed as having speech delay; =0 else.

Exhibit 7.4.1 Data Sources and Construction of Variables Used as Covariates in Analytical Models

		Data Sources			
Variable	**Description**	**Parent Interview**	**Medical Abstract**	**Computer Automated**	**Additional Details**
MatSTUTTER	Maternal stuttering	X	X		=1 if mother ever diagnosed as having stuttering; =0 else.
MatADHD	Maternal ADHD	X	X		=1 if mother ever diagnosed as having ADHD; =0 else.
MatTIC	Maternal tics (No mothers in this sample had this diagnosis. This variable not used in models.)	X	X		=1 if mother ever diagnosed as tics; =0 else.
Quadratic and Cubic Forms					
ChildAge2	*ChildAge^2 (squared)*	X	X		
ChildAge3	*ChildAge^3 (cubed)*	X	X		
PctPoverty1_2	(PctPoverty1/100) ^{2} (squared)	X			
PctPoverty1_3	(PctPoverty1/100) ^{3} (cubed)	X			
HOME_TotalIndex2	HOME_TotalIndex^2 (squared)	X			
HOME_TotalIndex3	HOME_TotalIndex^3 (cubed)	X			
Variables Used Only in Models for Finger Tapping Outcomes[a]					
Spline9	=1 if *ChildAge* > 9.0; =0 Else	X	X		
ChildAge_Spline9	*Childage * Spline9*	X	X		
ChildAge2_Spline9	*Childage^2 * Spline9*	X	X		

[a] Finger tapping tests for children aged 9 and above were slightly different than tests for younger children. Spline term allows for separate intercepts for children above and below 9 years. Spline*ChildAge and Spline*ChildAge2 terms allow for different age slopes for children above and below 9 years.

7.5. Imputation of Missing Values

The analysis data set contained no missing values on measures of ethylmercury exposure from thimerosal-containing vaccines and immune globulins. Having non-missing values on exposure measures was a requirement for inclusion in the study. The postnatal exposure measures were calculated as the amount of mercury contained in a received vaccine or immune globulin, divided by the child's weight at time of vaccine receipt, and summed over the appropriate age range. Thus, there was a requirement for data on each child's weight at the time of vaccine receipt. An explanation of imputation of missing weight data was provided in Section 7.2.2. To re-cap, linear interpolation was used if the missing weight value was between two known weight values, and predicted values from a growth-curve model were used as imputed values when missing weight values were not followed by recorded weight values. Children with no recorded weights were excluded from the analysis data set.

We did not conduct imputations for missing values on outcome measures. The consensus among the Principal Investigators at the CDC, the four participating HMOs, and Abt Associates, and the view shared by the study's External Expert Consultants, was that the analyses should be limited to records with non-missing values on outcome measures. Most of missing values on outcome measures were due to children not completing assessments when they became fatigued or emotional. In a few cases, the tests were administered incorrectly. For example, in some cases an incorrect basal or ceiling was used. On the finger tapping and grooved pegboard outcomes, some of the missing values were caused by equipment failures. Missing values on tics and stuttering outcomes occurred when parents or assessors failed to fill-out the relevant forms. On parent ratings of attention/executive functioning, and behavior regulation, some of the missing values were due to language barriers, i.e., when parents did not understand the instruments. A relatively large proportion of teachers failed to return rating forms for stuttering and for attention/executive functioning, and behavior regulation. The numbers of missing and non-missing values for each outcome measure are shown in Section 9.1.2., Exhibit 9.1.2.1.

In cases where there were missing values on covariate measures, we compared results from a single-imputation analysis methodology to a multiple-imputation methodology. Details follow.

There are two separate issues to consider in the imputation process. One is the method for obtaining an imputed value. Examples of methods include stochastic regression imputation, hot deck, cold deck, and mean value imputation. We used a stochastic regression imputation method, as described below. The second issue is whether the analysis is based on a single-imputation or on multiple-imputations.

In the single-imputation methodology, each missing value is replaced with a single imputed value, and the analysis proceeds as if the imputed data were comprised of actual, observed values. In multiple imputation, there are several (usually 5 or 10) imputed values calculated for each missing value. In our analyses we calculated 10 imputed values for each missing value. None of these several values are exactly equal to one another because there is a "random draw" component included in each of the imputed values. The multiple-imputation analysis uses the data from all 10 random draws. The advantage of multiple imputation is that it more fully accounts for the uncertainty arising from the use of imputed values in place of observed data. Its disadvantage is that it is more cumbersome to implement.

Our stochastic regression imputation method proceeded in the following manner. Suppose a variable, x_2, had several missing values. We fit a regression model to all of the non-missing values of x_2, where x_2 was the outcome variable and all other covariates in the data set were used on the right-hand side of the regression equation as independent (predictor) variables. We saved the residuals from this model in a data set. Next, using the parameter estimates from the fitted model, and the values on all of the other covariates in the data set, we calculated the predicted value of x_2, for each non-missing record in the data set. Let us call the predicted value x_2 of for child i, $\hat{x}_{2i}$,

Suppose child j had a missing value on the variable x_2. Let us denote the imputed value for child j as $\tilde{x}_{2j}$. To obtain the imputed value, we randomly selected a residual from the previously described data set of residuals. Let us denote the randomly selected residual value as r_{random}. We then calculated the imputed value as the sum of the predicted value obtained from the regression model, $\hat{x}_{2j}$, and the randomly selected residual, r_{random}. That is, $\tilde{x}_{2j} = \hat{x}_{2j} + r_{random}$. This is called stochastic regression imputation because the imputed value is obtained from the predicted value from a regression model and a random (stochastic) component. The reason for adding the randomly selected residual to the predicted value was to retain the same amount of variability in imputed values as exists in the observed values.

After completing the stochastic regression imputation process on all variables that had missing values, we obtained a data set with no missing values on covariates. The single-imputation analyses were based on that data set.

In the multiple imputation method, we created 10 data sets in the same manner as described above. Each data set was slightly different from one another because of the random component in each imputed value. In this method, our analysis models, (i.e., the models used to estimate the effects of ethylmercury exposure on outcomes), were fit to each of the 10 data sets. This resulted in 10 estimates for each model parameter, and 10 standard error estimates for each model parameter. The final estimate for a particular model parameter was calculated as the mean of the 10 separate estimates from the 10 data sets. And the final standard error for that parameter was calculated as a function of the mean of the standard errors estimated from the 10 regression models, a component

measuring the variation between the estimates obtained from the 10 regression models, and an adjustment factor for the 10 repetitions. A more formal explanation of the calculations used in the multiple imputation procedure follows.

We fit a model of the general form below to each of the D data sets, (D = 1, 2, … 10)
$Y_D = \beta_{0,d} + \beta_{1,d}x_{1,d} + \beta_{2,d}x_{2,d} + ...\beta_{k,d}x_{k,d} + \varepsilon_d$,

producing 10 estimates for each parameter
$\hat{\beta}_{0,1}, \hat{\beta}_{0,2}, ...\hat{\beta}_{0,10}$,
$\hat{\beta}_{1,1}, \hat{\beta}_{1,2}, ...\hat{\beta}_{1,10}$,
...,
$\hat{\beta}_{k,1}, \hat{\beta}_{k,2}, ...\hat{\beta}_{k,10}$,...

The final estimate for a parameter was calculated a the mean of the estimates from the 10 repetitions, e.g.,

$$\overline{\beta_1} = \frac{\sum_{d=1}^{10} \hat{\beta}_{1,d}}{10}$$

The standard error of the combined estimate, $s.e.(\overline{\beta})$, was calculated from a within-imputation variance component, and a between-imputation variance component, and an adjustment factor for the number of repetitions (D).

Let W_d be the estimated variance of the parameter from repetition d,

i.e., $W_d = [s.e.(\hat{\beta}_{1,d})]^2$.

The within-imputation variance was calculated as the average of the D=10 estimated variances

$$\overline{W_D} = \frac{\sum_{d=1}^{10} W_d}{10}.$$

The between-imputation variance component was calculated as

$$B_D = \frac{1}{D-1}\sum_{d=1}^{D}(\hat{\beta}_{1,d} - \overline{\beta_1})^2.$$

And the total was calculated as

$$T_D = \overline{W}_D + \frac{D+1}{D} B_D,$$

where (D+1)/D is the correction factor for D repetitions.

The standard error of $\bar{\beta}_1$ was calculated as $s.e.(\bar{\beta}) = \sqrt{T_D}$.

We applied both single-imputation and multiple-imputation methods to the main effects models corresponding to the study's primary research questions, and found that both methods produced very similar results. In two sets of results the parameter estimates were very similar, and the associations between exposure and outcome measures were statistically significant or non-significant for the same outcomes and exposure measures in both sets. These results are reported in Section 9.2.2.4.2. Since the analyses with the single-imputation were far less cumbersome, all subsequent analyses used the single-imputation methodology.

8. Analysis Approach

During the design phase of this study an analysis plan was developed that detailed what outcomes were to be measured, what the data sources would be, how exposure measures and covariates were to be coded, the forms of the statistical models that were to be fit to the data, and the method for deciding which covariates were to be retained or dropped for inclusion in the models for any particular outcome variable. The analysis plan went through several iterations of review and comment by the Principal Investigators at the CDC, at each of the four participating HMOs, and at Abt Associates, and by the study's External Expert Consultants[11]. Variable construction and the modeling approach followed very closely to that analysis plan. In the first phase of analysis, only models that were specified in the analysis plan were fit to the data. Following an agreed upon protocol, none of the preliminary results were shown to or discussed with anyone outside of the analysis team at Abt Associates prior to a meeting meeting that took place on April 8, 2005. At that meeting the preliminary results from those models were presented to the group of Principal Investigators and the study's External Expert Consultants. Those results generated new ideas and motivated new lines of inquiry. Subsequent to the meeting, requests to fit additional models came from the group of principal investigators and the External Expert Consultants. Consequently, many of the results presented in Section 9 are from models that were not specified in the original analysis plan. The analyses that were specified in the original analysis plan, and the analyses that were requested subsequent to the April 8, 2005 meeting are indicated in Exhibit 8.1.1.

The data sources and construction of measures were described previously in Sections 6 and 7. The remainder of Section 8 focuses on the analytical models used and on model selection (i.e., which covariates are included in each model). The design and analysis plans of the current study were strongly influenced by the Faroe Islands (Grandjean et al., 1997) and Seychelles Islands (Davidson et al., 1998) studies of the effects of dietary exposure to methylmercury during pregnancy on subsequent child outcomes. Consequently, the designs and methods implemented in those studies are frequently referenced in the discussion that follows.

Section 8.1 presents an example model specification and introduces notation that is used throughout the remainder of the report. The full set of models is documented in Section 9. The model specifications are presented in that section in order to clarify the interpretation of the results that are presented there.

Section 8.2 documents the methods used for model selection. Discussions of how we tested for effect modifiers, and how we approach the issue of multiple comparisons follow in Sections 8.3 and 8.4.

[11] See Acknowledgements section for listing of the Panel of External Consultants

Exhibit 8.1.1.
Explanation of Analyses That Were Specified in Original Analysis Plan, and Analyses That Were Requested Subsequent to Review of Preliminary Analysis Results.

Analyses Specified in Original Analysis Plan	Analyses Requested Subsequent to April 8, 2005 Meeting
Exhibit 9.2.2.1 Main Effect Models (1) and (2)	
Exhibit 9.2.2.2 Main Effect Models (1) and (2) with Multiple Imputation for Missing Values of Covariates	
	Exhibit 9.2.2.3 Main Effect Models (1) and (2) with Alternative Coding of Prenatal Exposure Variable
	Exhibit 9.2.2.4 Additional Main Effect Models for ADHD Outcomes
Exhibit 9.2.3.1. Summary of Thimerosal Effects for Females	
Exhibit 9.2.3.2. Summary of Thimerosal Effects for Males	
	Exhibit 9.2.4.1. Summary of Models Testing Effects of Cumulative Exposure Prenatal Through Seven Months – Full Data Set
	Exhibit 9.2.4.2. Summary of Models Testing Effects of Cumulative Exposure Prenatal Through Seven Months – Females
	Exhibit 9.2.4.3. Summary of Models Testing Effects of Cumulative Exposure Prenatal Through Seven Months – Males
	Exhibit 9.2.5.2. Summary of Multiple Sources of Prenatal Mercury Models
Exhibit 9.2.6.1. Summary of Models for Concurrent Antibiotics Effect –Birth to Seven Months	
Exhibit 9.2.6.2. Summary of Models for Concurrent Antibiotics Effect –Birth to 28 Days, and 29 Days to Seven Months	

Read Table: The results summarized in Exhibit 9.2.2.1 were from models that were specified in the original analysis plan. The results summarized in Exhibit 9.2.2.3 were from models that were requested subsequent to the presentation of preliminary analysis results that took place on April 8, 2005.

8.1. Overview of Analytical Models

In this section, we present an example model specification. This will allow us to introduce some notation and some terminology and conventions that will be used throughout the remainder of the document. The example model shown below is specified to produce estimates of the effects of prenatal exposure, neonatal (birth to 28 days) exposure, and cumulative exposure for the age range spanning 29 days to 217 days months (1 to 7 months), on an outcome measure, *Y*:

$$Y = \beta_0 + \beta_1 preNatThimer + \beta_2 HepB + \beta_3 Exp17mos + \sum_j \alpha_j oe_j + \sum_k \alpha_{j+k} cf_k + \sum_l \alpha_{j+k+l} St_l + \varepsilon$$

The model is specified as an ordinary least squares regression model. The outcome variable, *Y*, is assumed to be measured on a continuous scale. The error term, ε, is assumed to be conditionally independent and identically distributed normal with mean zero and variance σ^2.

There are three classes of right-hand-side variables in the model. The first class consists of the ethylmercury exposure variables. In this model, the *preNatThimer* variable is a measure of prenatal exposure to ethylmercury from thimerosal-containing vaccines and immune globulins, the variable *HepB* is a measure of exposure to Hepatitis B vaccines and immune globlins received in the first 28 days of life, and *Exp17mos* is a measure of exposure from vaccines received in the age range of one to seven months (29-214 days) (for details see Section 7.2).

The second class of right-hand-side variables represents other exposures. These are prenatal or postnatal exposures to neurotoxins that may be related to the outcome measures. We included this class of variables in the model in order to account for relationships between exposures to neurotoxins and the outcome measures, when making inferences about the effects of ethylmercury exposure on the outcome variable. Examples include maternal alcohol use and maternal smoking during pregnancy. These terms are represented in the model specification by oe_j, where "oe" stands for "other exposures", and the α_j represent fixed effect parameters. The summation symbol means that we will have 0, 1, 2, 3… up to "*J*" such terms in the model specification.

We have labeled the third class of right-hand-side variables as "child and family statistical control variables". This class of variables includes child and family demographic factors, birth conditions, child medical conditions, and maternal diagnoses. These are factors that we want to control for when making inferences about the relationship of ethylmercury exposure to the outcome variable. Examples include age and sex of the child, maternal age, and family socio-economic status. This class of variables is represented in the model specification by cf_k, where the subscript "k"

indicates that we will have 1, 2, 3, … up to "K" such terms in the model. The corresponding parameters are numbered "J + k", to indicate that the numbering follows sequentially, after the "other exposures" variables. For example, if there were two "other exposures" variables, then the first child and family statistical control variable in the model would be subscripted with a 3 (J + k = 2 + 1 = 3). The second *cf* variable would be numbered 4, (J + k = 2+2=4), etc.

The fourth class of variables in the model consists of site dummy variables. These are variables that indicate each of HMOs where data were collected. The site dummies are represented in the model specification by the terms St_l.

There are three hypotheses to be tested using the model shown in the example above. The first is the test of the null hypothesis that there is no linear relationship of prenatal ethylmercury exposure to the outcome variable. The second is a test of whether there is a relationship between receipt of Hepatitis B vaccines or immune globulins in the first 28 days of life, and the outcome measure. And the third is a test for a linear relationship between exposure to ethylmercury from vaccines received in the age range of one month to seven months, and the outcome variable. These are two-sided hypothesis tests, and we used a $p<0.05$ criterion for statistical significance. We use the following notation for these three tests.

$$H_0 : \beta_1 = 0 \quad vs \quad H_a : \beta_1 \neq 0,$$
$$H_0 : \beta_2 = 0 \quad vs \quad H_a : \beta_2 \neq 0,$$
$$H_0 : \beta_3 = 0 \quad vs \quad H_a : \beta_3 \neq 0.$$

Thirty five of the 42 outcomes analyzed in this study were measured on a continuous scale. The example model shown above was specified as a linear regression model, suitable for continuous outcome variables. Logistic regression models, that are analogous to the linear regression models shown here, were fit to the data for the 7 outcomes that were coded as binary measures.

8.2. Inclusion of Covariates

Consulting pediatricians, neurotoxicolgists, and other experts identified a long list of factors that were expected to have relationships with the neuropsychological measures that are the outcome variables in this study. It is not feasible to implement an experimental design that would strictly eliminate the potential influence of all of these factors on the outcome measures. However, by specifying some or all of them as covariates in our statistical models, we attempt to control for the influences of these factors on the outcome variables, when making inferences about the relationship between exposure to ethylmercury and the outcome measures.

In observational studies, selection of covariates can have a large impact on the inferences about exposure variables. Statisticians consulting on the design of the current study

(from External Expert Consultants, the CDC, the HMOs, and Abt Associates Inc.) suggested and discussed three different approaches to covariate selection. The three methods are not necessarily mutually exclusive. We will refer to the first method as the *a priori selection* method. In this approach, model covariates are selected during the design phase, well before data are collected. This method is based on the assumption that there is strong prior knowledge of the relationships between outcomes and the variables that are being considered as covariates and/or the relationships between ethylmercury exposure and the variables that are being considered as covariates. In many cases, strong prior knowledge exists. For example, for most of the outcome measures, we knew, a priori, that the age of the child at the time of testing would be related to the outcome.

We will refer to the second method as *backward elimination.* This is a very commonly used method of covariate selection in which one begins a step-wise process by fitting a model with a full set of covariates, and identifying the covariate with the largest p-value. That variable is dropped in the second iteration and a new model is fit, and the process is repeated. This procedure continues until all covariates that do not reach a pre-set significance criterion are dropped from the model.

Several consulting statisticians advocated the use of a *change-in-estimate* methodology. In this approach, the decision of whether or not to include a variable as a covariate is decided by fitting models with and without the covariate and comparing the estimates of the target parameter(s) (i.e., the exposure variables) in the two models. If the difference between the estimates from the two models of the target parameter(s) changes by more than some pre-determined cut-off level (e.g., 10%), then the covariate is retained in subsequent models, otherwise it is dropped.

Before considering the pros and cons of each approach, and describing the approach we used, we review the typical reasons that covariates are included in models. Then we review the covariate selection strategies used by Grandjean et. al (1997) for the Faroe Islands study, and by Davidson, et. al. (1998) for the Seychelles study. And we review a study by Budtz-Jorgensen et. al. (2007) that used the Faroe Islands data to compare the resulting inferences on exposure variables when several different covariate selection strategies were used.

Typically, covariates are included in regression models for any or all of the following three reasons:

- *To Reduce Residual Error and Increase Power.* To the extent that a covariate reduces the variance of the residual error, the power to detect a relationship between the exposure variables and the outcome measure will be increased. On the other hand, addition of covariates that are not related to the outcome measure can have the effect of decreasing the precision of the exposure estimates and, hence, decreasing power.
- *To Control for Confounding.* As an example of a confounder, suppose that for a particular outcome measure, lower maternal IQ was related to lower scores on the outcome measure. Furthermore, suppose there was a relationship between maternal IQ and exposure such that lower maternal IQ tended to be associated

with lower exposure. Then, in this scenario, maternal IQ is a confounder, and omission of the variable could lead to a spurious finding that lower exposure is related to lower scores on the outcome measure.

- *To Test for Effect Modification*. For example, suppose that biological differences between boys and girls were such that the neurocognitive development of boys was adversely affected by exposure to ethylmercury from vaccines or immune globulins, whereas girls were not sensitive to exposure. Then sex would be an effect modifier. If sex were an effect modifier, we would like to produce separate estimates of exposure effects for boys and girls. This is accomplished by adding sex-by-exposure interaction terms to the model. Without the interaction terms, the overall estimated exposure effect on both boys and girls combined would fall somewhere in between the two separate estimates. The sex variable could also be a confounder, if, for example, boys scored lower than girls regardless of their exposure and if the distribution of exposure levels was not the same for boys and girls.

The method for selecting covariates in the Faroe Island study is described by Budtz-Jorgensen et. al. (2007):

> "In the original analysis of the Faroese data Grandjean et al. (1997) developed an ad hoc criterion for confounder selection combining information across different outcome variables. According to this method the child's sex and age in addition to the maternal Raven score were considered obligatory confounders for all outcome variables. Additional confounders were selected approximately as follows. For each neuropsychological test important predictors were identified using backward elimination (adjusted for the obligatory covariates) with p=0.10. Predictors that were important for more than 3 outcomes (out of 17) were then included in the final regression model for all outcomes."

In the Seychelles study (Davidson, et. al., 1998), covariates were specified as part of the study design and were "selected because of their potential to bias the assessment of the association beween Hg and outcome". A full model and a reduced model were fit to the data for each outcome variable. The full model included all of the a priori selected covariates and the reduced model "included only those covariates that did not duplicate others or were felt to be the most relevant to child development in the Seychelles" (Marsh et. al, 1995).

Thus, the covariate selection strategy used in the Faroe Islands study was a mix of the *a priori* and *backwards elimination* methods. In the Seychelles study, the *a priori* method was used. None of the covariates used in the Faroe Islands study were tested as effect modifiers. In the Seychelles study, only one covariate, *sex*, was tested as an effect modifier. "Each full and reduced model was run both with and without mercury exposure by sex interaction terms to test the hypothesis that males and females have different mercury exposure slopes" (Davidson, et. al., 1998).

An attractive aspect of the *a priori* method of covariate selection is that it reduces the potential for criticism that the analysis will become some kind of data snooping exercise. That is, it completely precludes the possibility of an analyst choosing covariates in such a

way that the estimated exposure effects come as close as possible to some pre-conceived notion held by the analyst. A negative aspect of this approach is that you might end up specifying a model that does not fit the data well. And, if some of the covariates are not correlated with the outcome, the standard errors on the key exposure variables can be larger than they would have been had the non-significant covariate been eliminated. Furthermore, there may be potential confounders for which there is not enough prior knowledge for the decision of whether or not they should be included.

Backwards elimination methods are attractive from the point of view that they are often used and familiar. But use of this method using the conventional $p<0.05$ criterion has been criticized from the point of view that the selection criteria tends to favor covariates with strong relationships to the outcome, but may omit important confounders (i.e., variables that have a weaker relationship to the outcome, but have a strong relationship to exposure). Maldonado and Greenland (1993) evaluated a backwards elimination strategy and a change-in-estimate strategy using simulated data from a poisson regression model. They found that the p-value based method performed adequately when the alpha levels were higher than conventional levels (0.20 or more), and found that the change-in-estimate strategy performed adequately when the cut point was set to 10 percent. However, their data, generated from a poisson model, and their analysis model, with only a single covariate in addition to the key exposure variable, are very different than the models anticipated for the current study.

Using the Faroe Islands data, Budtz-Jorgensen et. al. (2007) compared several covariate selection strategies including backwards elimination, change-in-estimate, and the original covariate selection strategy used by Grandjean et. al. 1997. They looked at the backwards elimination strategy with three p-value cut-off levels, 0.05, 0.10, and 0.20, and, following the recommendation of Maldonado and Greenland (1993) used a 10% criterion for the change-in-estimate method. The measures that formed the basis of the comparisons were the standard errors and the biases on the exposure variables. To assess bias, they assumed that the full model with all 20 covariates produced an unbiased estimate of the exposure effect. Bias was defined to be the difference between the exposure coefficient estimated from the full model, and the coefficient estimated from the model with covariates selected with a competing selection approach. They compared results of the various selection strategies on models for two outcome variables. Both of these were also used as outcome measures in the current study (the California Verbal Learning Test, and the Boston Naming Test).

They found that, although the change-in-estimate strategy did an adequate job of identifying confounders and keeping them in the model, it sometimes threw out variables that were correlated with the outcome, but were not confounders. Therefore, this method threw out variables that, if retained, would have reduced the residual error and reduced the standard error of the exposure coefficient (thus increasing the power to detect exposure effects). Although they found that backwards elimination with a $p<0.05$ criterion was un-suited for confounder identification, they found that when the p-value criterion was set to $p<0.20$, backwards elimination strategy resulted in a reduction of residual error variance and did not throw out important confounders. They recommended

the backwards elimination strategy with a $p<0.20$ criterion over the change-in-estimate strategy. The original strategy used by Grandjean et. al. was comparable to the backwards selection strategy using the $p<0.20$ criterion in terms of reduction in bias and standard error of the exposure effect.

For the current study, we used a covariate selection method that was a mix of all three of the previously described methods, the a priori method, backwards elimination, and the change-in-estimate method. Our philosophical starting point was that if there were enough prior knowledge about all of the potential covariates then the ideal method for the current study would have been an a priori only method for the selection of covariates. We saw this as the ideal for the current study because a priori selection of covariates would allay fears on the part of stakeholders about potential post-hoc manipulation of the data to fit some prior notion. An a priori only method, however, was not practical for the current study because there were too many variables for which we did not have prior knowledge about their relationships to the outcome variables. This was especially true for the "other exposures" variables. Including a large number of covariates that are not related to the outcome, in the model, would have undesirable effects on the precision of the exposure estimates.

Our strategy for selecting covariates was as follows. We identified a set of a priori selected covariates that were included in all models for all outcomes. There was a second set of variables that were tested for inclusion. There were two ways that the testing could result in the determination that a particular variable would be retained in the final model for a particular outcome. The first way utilized the backwards elimination strategy using a $p<0.20$ cutoff. If the p-value for a particular variable was less that 0.20, then it was retained in the final model. Each variable was simultaneously evaluated using a change-in-estimate method with a 10 percent change criterion. When either method indicated that a particular variable should be retained as a covariate, then that variable was retained in the final model. This ensured that we did not drop variables that, if retained, would substantially reduce residual error variance, and ensured that we did not drop variables that are confounders.

We included dummy variables for HMO in all models. All but three of the remaining a priori selected covariates that were used in our study were used as covariates in the final models in both the Faroe Islands study and the Seychelles study. The three exceptions were age, child's computer experience, and the HOME score. Age was not used as a covariate in the Seychelles study, presumably because all of children tested were in a very narrow age range. The design of the current study was such that we tested subjects in the age range of 7 to 10 years. Age was expected to have a strong relationship to the outcome measures for the current study. Age was significant for both outcomes reported by Budtz-Jorgensen et. al. (2007). Computer experience was not used as a covariate in the Seychelles study because none of the outcome measures were based on a computer interactive assessment. In the Faroe Islands study, computer experience was an important predictor for the assessments that used a computer interactive testing regime. In the current study, computer experience was an a priori covariate only for those particular outcome measures that used a computerized assessment (the finger tapping and GDS

vigilance tasks). It was tested for inclusion in models for all other outcomes. Finally, the HOME scale score was not used in the Faroe Islands study. However, in the Seychelles study, it was a significant predictor at the $p<0.01$ level for five of the six outcomes, and significant at the $p<0.05$ level for the sixth.

In deciding which variables to treat as a priori selected, we looked at the statistical significance associated with each covariate as reported in Budtz-Jorgensen et. al. (2007), for the Faroe Islands study, and Davidson et. al. (1998), for the Seychelles Islands study. Budtz-Jorgensen et. al. (2007) showed significance levels for covariates for two outcomes and Davidson et. al. (1998) showed results associated with six outcomes. Exhibit 8.2.1 shows that, with the exceptions of age, child's computer experience, and the HOME score, our a priori selected covariates were statistically significant at a $p<0.20$ criterion for at least four of the six total outcomes shown in the two papers.

For each outcome variable, the remaining covariates shown in Exhibit 8.2.1 were tested for inclusion in the final model. These include variables that were used in the Faroe and the Seychelles studies, but that were not consistently found to be confounders or reducers of residual in those studies. These also include variables that were not examined in the Faroe or Seychelles studies, but that had been suggested by consulting neurologists, toxicologists or pediatricians because of their hypothesized relationship to the outcome measures. We also tested higher order functional forms of age, percent poverty, and the HOME score for inclusion. We included tests for these forms because, for example, we did not know, a priori, whether a linear coding of the age variable would be the most appropriate functional form to assume for each outcome measure. For some outcome measures, quadratic or cubic forms of these variables significantly improved the fit.

The variable selection routine was implemented for each outcome measure using the main effect model for prenatal exposure and cumulative exposure during the age range from birth to 7 months (See Model 1, of Section 9.2.2.2 for specifications of this model). For each outcome measure, variables that were selected for inclusion in that model were retained as covariates in all other models for that outcome measure. All models for any one particular outcome measure used the same covariate set. However, the selection process was such that different outcome measures had different covariate sets. The list of covariates that were used in models for each outcome measure is shown in Exhibit 8.2.2.

Exhibit 8.2.1. A Priori Variables and Variables Tested for Inclusion as Model Covariates

Variable	Description / Levels	Research Evidence	
		Faroe Islands[a]	Seychelles Islands[b]
Variables Included in Every Model (a priori selected)			
ChildAge	Child Age (Yrs) at assessment	2/2[c]: p=.20 2/2: p=.05	Not entered
sexmale	Sex of child 0=female, 1=male	2/2: p=.20 0/2: p=.05	4/6: p=.20 3/6: p=.05
Birth weight	1 = if birth weight 2500-2999 grams 2 = Birth weight 3000-3999 grams 3 = Birth weight 4000+ grams	2/2: p=.20 1/2: p=.05	4/6: p=.20 3/6: p=.05
Maternal IQ	1= Score in lower third of distribution 2= Score in middle third of distribution 3= Score in upper third of distribution	2/2: p=.20 2/2: p=.05	4/6: p=.20 3/6: p=.05
HOME_TotalIndex	"HOME" Total Index	Not entered	6/6: p<.05
PctPoverty1	(Percent of poverty line)/100	SES[d]: 2/2: p=.20 2/2: p=.05	SES[d]: 5/6: p=.20 5/6: p=.05
Maternal Education	0= No HS degree 1=High school diploma or GED 2=attended some college, but no degree 3=Associate's degree or higher	SES[d]: 2/2: p=.20 2/2: p=.05	SES[d]: 5/6: p=.20 5/6: p=.05
SingleParent	Child lives in a single parent household (0/1)	SES[d]: 2/2: p=.20 2/2: p=.05	SES[d]: 5/6: p=.20 5/6: p=.05
Site	HMO-A HMO-B HMO-C HMO-D		
Variables Tested for Inclusion: Child and Family Characteristics			
Computer Experience	0=No experience 1=some experience 2=much experience.	**Computerized tests:** p=.05	
Maternal Age	1= Maternal Age at Ch Birth: <=16 years 2=Maternal Age at Ch Birth: 17-39 years 3=Maternal Age at Ch Birth: >=40 years	1/2: p=.20 0/2: p=.05	1/6: p=.20 1/6: p=.05
OlderSibs	Child has an older sibling (0/1)	1/2: p=.20 0/2: p=.05	Not entered
YoungerSibs	Child has a younger sibling (0/1)	1/2: p=.20 0/2: p=.05	Not entered
DayCareCentr	# of center-based day care settings prior to KG	1/2: p=.20 1/2: p=.05	Not entered
DayCareHome	# of home-based day care settings prior to KG	1/2: p=.20 1/2: p=.05	Not entered
EngOnly	English only at home	Not entered	full model only/ ? signif.[e]
Breast Feeding (Duration)	0 = Breast Fed: <1mo 1 =Breast Fed: 1-6mos 2 = Breast Fed: 6+ mos	0/2: p=.20 0/2: p=.05	full model only/ ? signif.[e]
Variables Tested for Inclusion: Child Birth Conditions			
cMedicalHist_1	=1 if birth headCM +/- 2SD from Mean	Not entered	2/6[e]: p=.20 0/6: p=.05

Exhibit 8.2.1. A Priori Variables and Variables Tested for Inclusion as Model Covariates

Variable	Description / Levels	Research Evidence	
		Faroe Islands[a]	Seychelles Islands[b]
C5APGARImpVal1	5-minute apgar		
Variables Tested for Inclusion: Prenatal Exposures (non-vaccine related)			
PreNatNicotine_1	Used tobacco during pregnancy	0/2: p=.20 0/2: p=.05	full model only/ ? signif.[f]
PreNatAlcohol_1	0=never - 4 heavy	Not entered	full model only/ ? signif.[f]
Tuna Consumption	0= no consumption of tuna during pregnancy. 1 = moderate consumption (less than one serving/week) 2 = high consumption (more than one serving per week)		
PreNatFish_1	1= if mother reported eating tuna, and ocean fish, and home-caught fish during pregnancy. 0 = else.		
PreNatOrgMerc_1	Use of mercury-containing contact lens solutions or nasal sprays during pregnancy.		
PreNatHomePro_1	Prenatal exposure to mercury from home products		
Tooth Amalgams	0 = mother had no amalgam fillings during pregnancy 1 = had amalgam fillings, but no dental work and did not chew gum during pregnancy 2= had amalgam fillings and had dental work or chewed gum during pregnancy.		
PreNatlead_1	Prenatal exposure to lead from occupational or residential sources		
PreNatIllDrug	1=Cocaine or Narcotic		
Variables Tested for Inclusion: Child Medical Conditions			
IronDef_1	Anemia or iron deficiency		
ADHDstimulant	Use of ADHD stimulant in 12 hours prior to assessment		
ChdPICA_1	Child Pica		
Variables Tested for Inclusion: Maternal Diagnoses			
MatLangDel	Maternal Language Delay		
MatSpeechDel	Maternal speech delay		
MatSTUTTER	Maternal stuttering		
MatADHD	Maternal ADHD		
MatTIC	Maternal tics		
Variables Tested for Inclusion: Quadratic and Cubic Forms			
ChildAge2	ChildAge**2 (squared)		
ChildAge3	ChildAge**3 (cubed)		
PctPoverty1_2	(PctPoverty1/100)**2 (squared)		
PctPoverty1_3	(PctPoverty1/100)**3 (cubed)		
HOME_TotalIndex2	HOME_TotalIndex**2 (squared)		
HOME_TotalIndex3	HOME_TotalIndex**3 (cubed)		

[a] Budtz-Jorgenson et al. (2007) *Confounder Identification in Environmental Epidemiology*. Assessment of Health effects of Prenatal Mercury Exposure.

[b] Davidson et al. (1998). *Effects of prenatal and postnatal methylmercury exposure from fish consumption on neurodevelopment. Outcomes at 66 months of age in the Seychelles Child Development Study*. JAMA 280(8): 701-707.

[c] Notation represents number of outcomes for which covariate was significant. For example, "½" should be interpreted to mean that the covariate was significant for 1 of the 2 outcomes that were tested.

[d] In Faroe Island study, a single measure of socio-economic status (the Hollingsead) was used. In Seychelles study SES variables were paternal employment, paternal education, and maternal education.

[e] In Davidson et. al, this variable took the value "1" if child had intrauterine growth retardation (IUGR) or if head size was > 2 standard deviations from mean at birth. In the current study, IUGR was an exclusionary condition.

[e] These covariates were included in the full model only. Their level of significance was not reported.

Exhibit 8.2.2. Covariates Used in Models for Each Outcome Measure

	Age	SexMale	Birth Wt.	Matern. IQ	Home	Pct Pov	Mat. Educ	Single Par.	Site	Comp Exp.	Mat Age	Older Sib	Young. Sib	DayCenter	DayHome	Eng Only	B Feed Dur	cMed Hist	Apgar	Pre Nicotine	Pre Alcohol	Pre Tuna	Pre Fish	Pre Org Mer	Pre HomePr	Amalgams	Pre Lead	Pre Ill Drug	Iron Def	ADHD Stim	Chld Pica	Mat Lang	Mat Speech	Mat Stutt	Mat ADHD	Mat Tic	Age2	Age 3	PctPov2	Pct Pov3	Home2	Home3	Spline	Spline*Age	Spline*Age2
Speech and Language																																												
Boston Naming Test	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X					X			X	X						X	X										
NEPSY: Speeded Naming	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X		X	X		X		X	X	X	X				
NEPSY: Comprehension of Instructions	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X		X	X	X					
CELF: Formulated Sentences	X	X	X	X	X	X	X	X	X	X		X		X		X	X	X											X			X		X			X	X	X	X				
CELF: Recalling Sentences	X	X	X	X	X	X	X	X	X			X				X	X		X		X		X				X		X				X	X	X	X		X	X					
GFTA: Articulation (lower = better)	X	X	X	X	X	X	X	X	X			X							X		X								X			X	X		X				X	X				
Stuttering: Assessor Rating (lower = better)	X	X	X	X	X	X	X	X	X												X						X							X		X	X	X	X					
Stuttering: Parent Rating (lower = better)	X	X	X	X	X	X	X	X	X																																			
Stuttering: Teacher Rating (lower = better)	X	X	X	X	X	X	X	X	X	X			X					X			X		X									X							X	X					
Verbal Memory																																												
CVLT-C: Free Recall, No Delay	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X	X	X		X	X							
CVLT-C: Free Recall, Short Delay	X	X	X	X	X	X	X	X	X						X	X		X			X	X					X					X					X		X						
CVLT-C: Cued Recall, Short Delay	X	X	X	X	X	X	X	X	X			X	X		X	X		X	X						X							X	X				X								
CVLT-C: Free	X	X	X	X	X	X	X	X	X				X	X	X	X	X	X	X			X		X	X		X			X		X					X		X						

Exhibit 8.2.2. Covariates Used in Models for Each Outcome Measure

	Age	SexMale	Birth Wt.	Matern. IQ	Home	Pct Pov	Mat. Educ	Single Par.	Site	Comp Exp.	Mat Age	Older Sib	Young. Sib	DayCenter	DayHome	Eng Only	B Feed Dur	cMed Hlst	Apgar	Pre Nicotine	Pre Alcohol	Pre Tuna	Pre Fish	Pre Org Mer	Pre HomePr	Amalgams	Pre Lead	Pre Ill Drug	Iron Def	ADHD Stim	Chld Pica	Mat Lang	Mat Speech	Mat Stutt	Mat ADHD	Mat Tic	Age2	Age 3	PctPov2	Pct Pov3	Home2	Home3	Spline	Spline*Age	Spline*Age2
Recall, Long Delay																																												
CVLT-C: Cued Recall, Long Delay	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X					
CMS Stories 1: Immediate Recall	X	X	X	X	X	X	X	X	X	X		X		X			X										X					X					X	X							
CMS Stories 2: Delayed Recall	X	X	X	X	X	X	X	X	X			X		X	X	X	X						X	X			X		X			X		X	X		X	X	X	X					
Achievement																																												
WJIII: Letter-Word Identification	X	X	X	X	X	X	X	X	X	X		X	X			X	X				X		X	X			X						X			X	X	X						
Fine Motor Coordination																																												
Grooved Pegboard: Dominant Hand (lower = better)	X	X	X	X	X	X	X	X	X						X	X	X	X			X		X	X								X										X			
Grooved Pegboard: Non-dom Hand (lower = better)	X	X	X	X	X	X	X	X	X		X	X		X	X	X	X	X	X	X	X	X		X	X	X		X		X		X		X		X		X				X	X	X
Finger Tapping: Dominant Hand	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X														X			X		X								
Finger Tapping: Non-dominant Hand	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X			X		X		X	X	X					X			X		X	X	X						
Visual Spatial Ability																																												
Stanford Binet: Copying	X	X	X	X	X	X	X	X	X	X	X	X			X	X		X	X	X	X	X	X			X			X			X					X	X	X	X					
Attention/ Executive Functioning																																												
GDS Vigilance Task: Correct	X	X	X	X	X	X	X	X	X	X	X	X		X	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X		X	X	X						

Exhibit 8.2.2. Covariates Used in Models for Each Outcome Measure

	Age	SexMale	Birth Wt.	Matern. IQ	Home	Pct Pov	Mat. Educ	Single Par.	Site	Comp Exp.	Mat Age	Older Sib	Young. Sib	DayCenter	DayHome	Eng Only	B Feed Dur	cMed Hist	Apgar	Pre Nicotine	Pre Alcohol	Pre Tuna	Pre Fish	Pre Org Mer	Pre HomePr	Amalgams	Pre Lead	Pre Ill Drug	Iron Def	ADHD Stim	Chld Pica	Mat Lang	Mat Speech	Mat Stutt	Mat ADHD	Mat Tic	Age2	Age 3	PctPov2	Pct Pov3	Home2	Home3	Spline	Spline*Age	Spline*Age2
Responses																																												
GDS Vigilance Task: Errors (lower = better)	X	X	X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X	X		X					X	X	X	X	X	X	X		X	X	X	X					
WISC III: Digit Span, Forward Recall	X	X	X	X	X	X	X	X	X	X	X	X					X		X	X	X		X		X		X			X		X		X		X	X	X	X					
WISC III: Digit Span, Backward Recall	X	X	X	X	X	X	X	X	X								X	X										X		X					X										
WISC III: Digit Span, Combined	X	X	X	X	X	X	X	X	X			X					X	X	X				X				X	X		X		X			X				X	X					
BRIEF Parent Rating: Metacognition (lower = better)	X	X	X	X	X	X	X	X	X	X				X	X	X		X	X	X	X	X		X	X		X			X	X	X			X		X	X							
BRIEF Teacher Rating: Metacognition (lower = better)	X	X	X	X	X	X	X	X	X		X			X	X	X	X	X	X	X	X	X		X	X	X	X			X				X	X		X		X						
Behavior Regulation (lower = better)																																												
CRS-R: Parent Rating: Hyperactive/Impulsive	X	X	X	X	X	X	X	X	X		X	X		X	X		X			X	X				X					X	X				X				X						
CRS-R: Teacher Rating: Hyperactive/Impulsive	X	X	X	X	X	X	X	X	X					X		X	X	X	X			X		X					X									X							
CRS-R: Parent Rating: Inattentive	X	X	X	X	X	X	X	X	X	X				X	X	X		X		X	X	X	X							X	X	X			X		X		X						
CRS-R: Teacher Rating: Inattentive	X	X	X	X	X	X	X	X	X	X					X		X	X		X	X	X			X	X				X		X			X										
BRIEF Parent Rating: Behavior	X	X	X	X	X	X	X	X	X			X		X	X			X		X	X	X			X					X	X				X				X						

Exhibit 8.2.2. Covariates Used in Models for Each Outcome Measure

	Age	SexMale	Birth Wt.	Matern. IQ	Home	Pct Pov	Mat. Educ	Single Par.	Site	Comp Exp.	Mat Age	Older Sib	Young. Sib	DayCenter	DayHome	Eng Only	B Feed Dur	cMed Hist	Apgar	Pre Nicotine	Pre Alcohol	Pre Tuna	Pre Fish	Pre Org Mer	Pre HomePr	Amalgams	Pre Lead	Pre Ill Drug	Iron Def	ADHD Stim	Chld Pica	Mat Lang	Mat Speech	Mat Stutt	Mat ADHD	Mat Tic	Age2	Age 3	PctPov2	Pct Pov3	Home2	Home3	Spline	Spline*Age	Spline*Age2
Regulation																																												
BRIEF Teacher Rating: Behavior Regulation	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X				X		X			X				X	X		X		X	X				
Tics (lower = better)																																												
Motor tics (current): Assessor Rating	X	X	X	X	X	X	X	X	X	X				X	X		X	X	X		X	X	X		X				X					X		X	X	X	X				
Phonics tics (current): Assessor Rating	X	X	X	X	X	X	X	X	X						X						X	X	X		X													X	X				
Motor tics (current): Parent Rating	X	X	X	X	X	X	X	X	X			X		X		X			X	X		X	X	X	X			X	X				X	X	X		X	X	X	X				
Phonics tics (current): Parent Rating	X	X	X	X	X	X	X	X	X					X			X	X		X	X	X			X		X	X					X		X		X	X	X	X				
General Intellectual Functioning																																											
WASI Verbal IQ	X	X	X	X	X	X	X	X	X	X		X	X	X		X	X		X				X							X	X	X		X										
WASI Performance IQ	X	X	X	X	X	X	X	X	X	X			X	X		X	X						X						X	X														
WASI Full Scale IQ	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X		X	X			X						X	X		X		X	X		X	X	X					

"X" indicates that the variable shown in the column was used as a covariate in all models for the outcome variable shown on the row.

8.3. Testing for Effect Modifiers

The test for whether a covariate is an effect modifier involves creating an interaction term between the covariate and the exposure variables, and conducting tests of the null hypotheses that the coefficients for the interactions term are zero. Grandjean et. al. (1997), did not test for effect modifiers. Davidson et. al. (1998) tested for interactions between sex and exposure and found a significant sex-by-prenatal exposure interaction for one of their six outcome measures. Following the lead of Davidson et. al., (1998), our analysis plan specified models to test for sex-by-exposure interactions.

Additionally, several studies of the rates of excretion of methylmercuric chloride in rodents have indicated that oral antibiotics taken concurrently with oral ingestion of methylmercuric chloride is associated with slower excretion (Rowland et. al., 1977, 1980,1984). It has therefore been suggested that if children are on antibiotics at the time of exposure to ethylmercury from thimerosal-containing vaccines or immuned globulins, that the antibiotic use could act as a modifier of an exposure effect. Therefore, we included specifications for models to test for these interaction effects in the analysis plan.

The current report also includes results from two models with tests for effect modification that were not included in the original analysis plan. The requests for these analyses were generated after the April 8th, 2005 presentation of preliminary results to group of Principal Investigators and the study's External Expert Consultants. One is a test for an interaction effect between prenatal and postnatal exposure to ethylmercury from thimerosal-containing vaccines and immune globulins. This test was motivated by a theory that prenatal exposure could exacerbate the effects of postnatal exposure. Details are provided in Section 9.2.4.

A second model is similar to the first except that the measure of prenatal exposure includes exposures to mercury from sources other than vaccines and immune globulins. The other sources include prenatal mercury exposures from consumption of fish, from mercury-containing contact lens and nasal spray solutions, from home products, and from dental amalgams. Details are provided in Section 9.2.5.

8.4. Multiple Testing

We fit models to data for 42 outcome variables. The example model specified in Section 8.1 produces three hypothesis tests. Multiplying the three hypothesis tests by the 42 outcomes results in 126 hypothesis tests. A similar model to the one presented in the example, but where a test for the effect of cumulative exposure in the age range of birth to 7 months replaces the two separate terms for birth to one month, and 1 to 7 months in the example model, was fit to all 42 outcomes. Multiplying the two hypothesis from this model by the 42 outcomes results in 84 additional tests. Furthermore, separate estimates were calculated for boys and girls, resulting in yet more tests. During the design phase, we tried to limit the proliferation of statistical tests by focusing on a few key research questions, and a few model specifications to answer those questions. However, the number of tests inevitably multiplied

after the presentation of preliminary results motivated interest in additional analyses. Across all of the models that were fit to the 42 outcome variables, Section 9 reports results of more than 2,500 hypothesis tests.

With such a large number of tests, we expect to see a large number of statistically significant results that are due to chance alone. During the design phase we considered the use of methods, such as a Bonferonni adjustment to control for the overall type I error rate. However, the group of Principal Investigators and the study's External Expert Consultants were not in favor of such an adjustment. Their recommendations were to report the conventional levels of statistical significance with appropriate caveats in the written text regarding the number of tests that were performed.

8.5. Reporting Effect Sizes

In addition to reporting the parameter estimated and standard errors corresponding to the exposure variables from the linear and logistic regression models, we sought to present measures that could be interpreted and compared as measures of effect size. In order to facilitate comparisons of effect sizes from the current study to the methylmercury effects reported from the Faroe Islands study, we followed the lead of Jacobson (2001) who had converted the raw regression coefficients reported by Grandjean et. al. (1997) into standardized regression coefficients. The standardized regression coefficient is calculated by multiplying the estimated regression coefficient from the model (the unstandardized coefficient) by the ratio of the standard deviation of X (the exposure variable) to the standard deviation of Y (the outcome variable). This calculation is equivalent to standardizing all independent and dependent variables in the model and fitting a model to the standardized variables[12]. The raw and standardized regression coefficients reported by Jacobson (2001) for the Faroe Islands results are shown in Exhibit 8.5.1.

An odds ratio is a standardized measure of effect size. The parameter estimates for the logistic regression models are easily converted to odds ratios by taking their exponent. However, this simple procedure produces the odds ratio of the outcome associated with a one-point increase in the exposure measure. Since a one-point increase in exposure does not have any intuitive meaning, we converted the standardized result to be the odds ratio associated with a two standard deviation increase in the exposure measure. We chose two standard deviations of the exposure measure to roughly correspond to the difference between low and high exposure.

[12] A proof is provided by R. William at: http://www.nd.edu/~rwilliam/xsoc592/lectures/x92.pdf.

Exhibit 8.5.1. Results Reported by Jacobson (2001) for Faroe Islands Data				
Exposure SD	Endpoint	Endpoint S.D.	Raw Regression Coefficient	Standardized Regression Coefficient
0.375	Finger Tapping	6.15	-1.10	-0.07
	CPT Errors	0.54	0.12	0.08
	CPT Reaction Time	80.00	40.30	0.18
	Digit Span	1.50	-0.27	-0.06
	Boston Naming Test: no cues	5.30	-1.77	-0.12
	Boston Naming Test: cues	5.30	-1.91	-0.13
	CVLT short-term recall	3.10	-0.57	-0.06
	CVLT long-term recall	3.80	-0.55	-0.05

9. Results

9.1. Descriptive Statistics

We present two sets of descriptive statistics. The first set is provided in order to describe the characteristics of the study participants, the variation across the four HMOs from which the sample was drawn, and for some variables, comparisons to national population means. The second set specifically describes the variables used in the analysis models. The former draws on information that illuminates information on who the study participants were, but includes variables or forms of variables that were not part of the analytic models. For example, the first section presents the proportions of participants that were 7, 8, 9, and 10 years old at the time of assessment. However, the analytic models did not utilize a categorical age variable. For the models, age was a continuous variable with values that ranged from 7.07 to 10.99. The continuous age variable is described in the second section.

9.1.1. Characteristics of the Analysis Sample

9.1.1.1. Demographics

The sampling method was designed to obtain a sample with a wide distribution of exposures for the neonatal period (1-28 days), and early infancy (29-214 days). The method did not include explicit stratification on age of child, but included implicit stratification on age via a systematic sampling routine (see Section 5.5 for details). This method increases the probability that children in all age ranges will be included in the sample. Exhibit 9.1.1.1 shows the proportions of assessed children at each of the four HMOs that were 7, 8, 9, and 10 year-old children. In the total sample, and at each of the four HMOs, roughly half of the study participants were boys, and roughly half were girls. The birth weights of almost three quarters of study participants were between 3 and 4 kilograms. Children with birth weights that were below 2.5 kilograms were excluded from the study.

The maternal IQ score was a population-normalized measure with a mean of 100 and a standard deviation of 15. Approximately 16 percent of the national population has IQ scores below 85 (one standard deviation below the mean), and approximately 16 percent has IQ scores above 115 (one standard deviation above the mean). Exhibit 9.1.1.1 shows that the distribution of IQ scores in the total sample was slightly skewed towards higher scores than the national population. Cumulative exposures from birth to seven months varied across maternal IQ levels ($p<0.001$). Higher maternal IQ was associated with higher exposure levels.

The mothers of participants also appeared to have higher educational attainment, on average, than the national population. Nationally, in 2003, around 87 percent of women between the ages of 25 and 40 had a high school degree or above, 57 percent had some college or more, and roughly 30 percent had bachelor's degrees (Stoops, 2004). In the total sample, about 96 percent had a high school degree or above, 79 percent had some college or more, and although not directly comparable to the national numbers, about one half of the mothers of participants reported having associate's degrees or above. Higher maternal education level was associated with higher cumulative exposures from birth to seven months ($p<0.001$).

An eligibility criterion for the study was that children must live with their biological mothers at least four days per week. In the total sample, 19 percent of focus children lived in single parent households, i.e., lived with their mother but not with their father. Living in single parent household was associated with lower exposure levels ($p<0.01$). Seven percent of the focus children were born to mothers who were 40 years or older at the time of birth of the child, and 63 percent lived in household where English was the only language spoken. Older maternal age and English language households were associated with higher exposure levels ($p=0.05$, and $p<0.001$, respectively).

Exhibit 9.1.1.1 Descriptive Statistics for Demographic Measures

			By Cumulative Exposures Birth to 7 Months			
		Full Sample	**0 - 62.5 μg**	**75 – 137.5 μg**	**150.0 – 187.5 μg**	
		n=1047	**n=93**	**n=691**	**n=263**	
Demographics		Percent	**Percent**	**Percent**	**Percent**	**P-value[b]**
Child Age (Years):	7	17	18	16	17	0.33
	8	23	26	23	22	
	9	28	35	28	28	
	10	32	20	33	33	
Sex:	Male	49	54	48	48	0.57
Birth weight:	2500-2999 grams	11	11	10	15	0.34
	3000-3999 grams	73	75	75	69	
	4000+ grams	15	14	15	16	
Maternal IQ:	<85	10	12	12	5	<0.001
	85 – 115	73	73	75	66	
	>115	17	15	13	29	
Maternal Education:	No High School degree	4	3	5	2	<0.001
	High School /GED[a]	16	16	18	10	
	Some College	28	38	29	24	
	College degree	51	43	48	65	
Child lives in a single parent household		19	29	21	13	0.008
Maternal Age (at Child's Birth):	16-39 years	93	91	94	89	0.050
	>=40 years	7	9	6	10	
Only English spoken at home		63	63	58	75	<0.001

Sample size = 1,047 assessed children.

[a] GED is a certificate given for the completion of the Tests of General Educational Development, a series of five tests. It is the equivalent of a high school diploma.

[b] P-value is from chi-square test of independence between the demographic characteristic and the three levels of cumulative exposure.

Read Table: Seventeen percent of children were 7 years-old at the time of assessment. Eighteen percent of low exposure children (**0 - 62.5 μg**) were 7 years-old at the time of assessment.

9.1.1.2. Outcomes

Exhibit 9.1.1.2 provides a basis for comparison between the study sample and the national population of children of the same age on assessment results. The results indicate that for most of the measures that have national norms, the sample of study participants scored higher, on average, than the national population. For example, the WASI measures of general intellectual functioning are standardized such that the national population mean and standard deviation are 100 and 15, respectively. The last columns in the exhibit show the means for the full sample, i.e. children from all four HMOs. The means for the three measures range from around 105 to 107. Thus this sample of children scored 5 to 7 points, or roughly a third of a standard deviation unit, higher than the national average on these measures. The variation among the scores of children in the sample was similar to the variation in test scores that would be obtained from a national sample. That is, the standard deviations of the measures are close to the standard deviations expected from a national sample.

For most of the speech and language measures the sample means were roughly a tenth to a half a standard deviation unit higher than the national population means. On three of the four parent ratings of behavior regulation and attention/executive functioning, the sample children had slightly higher scores than the national population. On these measures higher scores indicate the presence of a greater number of undesirable behaviors or symptoms. On one measure their average scores were slightly lower.

The exhibit also shows the variation of means among HMOs. Children from HMOs C and D tended to have higher average scores on general intellectual functioning, achievement, language, and memory measures than children assessed at HMOs A and B.

Exhibit 9.1.1.2
Means and Standard Deviations on Normed Tests for Sample By HMO

	HMO									
	HMO-A		HMO-B		HMO-C		HMO-D		Total (n = 1047)	
Tests with Standardized Score for National Norming Sample: Mean = 100; Standard Deviation = 15										
Measure[a]	**x**	**s.d.**	**x**	**s.d.**	**x**	**s.d.**	**x**	**s.d.**	**x**	**s.d.**
General Intellectual Functioning										
WASI Full Scale IQ	106.3	14.3	104.4	13.3	111.7	15.0	116.1	15.3	107.4	14.6
WASI Performance IQ	105.7	15.1	101.7	14.3	108.2	15.2	110.9	17.1	105.1	15.3
WASI Verbal IQ	106.7	14.3	103.6	13.3	111.5	14.5	114.9	16.2	107.1	14.6
Achievement										
WJR Letter-Word	108.1	11.2	105.8	11.1	106.4	13.0	110.4	11.5	107.0	11.7
Measures with Standardized T-Scores: Mean = 50 and Standard Deviation = 10										
Memory for Words	**x**	**s.d.**	**x**	**s.d.**	**x**	**s.d.**	**x**	**s.d.**	**x**	**s.d.**
CVLT: Free Recall, No Del.	53.9	9.7	53.5	10.2	54.4	9.9	56.5	9.3	54.0	9.9
Parent Ratings of Behavior Regulation										
Connors Inattention	51.7	10.4	52.4	10.6	52.3	10.0	51.7	11.6	52.1	10.5
Connors Hyperactivity	53.7	10.6	54.9	11.4	53.7	10.0	52.9	11.5	54.1	10.9
Parent Ratings of Attention/Executive Functioning										
BRIEF Meta-cognition	51.0	10.7	51.6	11.6	51.4	10.8	49.0	12.6	51.2	11.2
BRIEF Behavioral Control	48.7	10.2	49.7	10.7	49.4	10.3	47.2	11.2	49.1	10.5
Tests with Standardized Score for National Norming Sample: Mean = 10; Standard Deviation = 3										
Language Use	**x**	**s.d.**	**x**	**s.d.**	**x**	**s.d.**	**x**	**s.d.**	**x**	**s.d.**
NEPSY Speeded Naming	10.2	2.7	10.0	2.7	10.9	2.7	11.2	2.7	10.4	2.7
NEPSY Compren of Instr	10.9	2.7	10.2	2.9	11.6	2.6	11.9	2.5	10.9	2.8
CELF-3 Formulated Sent	11.0	2.6	10.6	2.6	11.6	2.9	11.6	2.7	11.0	2.7
Memory for Connected Text										
CMS Short-term Memory	10.7	3.0	10.6	3.0	11.5	2.9	12.3	2.8	10.9	3.0
CMS Long term Memory	11.0	3.0	10.7	3.0	11.5	3.0	12.4	2.9	11.1	3.0
Tests with Standardized Score for National Norming Sample: Mean = 0; Standard Deviation = 1										
Verbal Memory	**x**	**s.d.**	**x**	**s.d.**	**x**	**s.d.**	**x**	**s.d.**	**x**	**s.d.**
CVLT Free ST	0.4	1.0	0.5	1.0	0.4	0.9	0.5	1.0	0.4	0.9
CVLT Cued Free ST	0.5	1.0	0.5	1.0	0.6	1.0	0.7	1.0	0.5	1.0
CVLT Free LT	0.5	0.9	0.5	0.9	0.6	0.9	0.6	0.9	0.5	0.9
CVLT Cued Free LT	0.4	0.9	0.5	0.9	0.6	0.9	0.7	0.9	0.5	0.9

9.1.1.3. Exposures

The postnatal exposure measures used in the analytical models were calculated as micrograms of ethylmercury divided by weight of the child (in kilograms) at the time of receipt of the vaccine or immune globulin, and summed over the relevant time period (i.e., 0-28days, 29-214 days, or 0-214 days). Those measures are described in the Section 9.2. In the current section we describe postnatal exposures without the division by child's weight. These latter measures are useful for descriptive purposes because they are easier to relate to the mercury amounts contained in individual vaccines. A single dose of most childhood vaccines in use during the mid to late 1990s contained 0, 12.5, or 25 micrograms of ethylmercury. Thus, an exposure amount equal to, for example, 37.5 micrograms, implies receipt of either three vaccines that each contained 12.5 micrograms of mercury, or receipt of two vaccines, one containing 12.5 micrograms, the other containing 25 microgram of ethylmercury.

The leftmost panel of Exhibit 9.1.1.3 shows the frequency distribution of cumulative exposure during the age range from birth to 7 months. It shows, for example, that 16 of the study children had zero micrograms of exposure during this age range. The middle panel of the exhibit shows neonatal exposures (1-28 days) crossed with cumulative exposure during the age range from one to seven months (29-214 days). It shows, for example, that three children had a birth dose of HepB (12.5 μg during the age range 0-28 days), but had zero exposure during the age range spanning 29-214 days. The column totals of the middle panel show that 312 of the study participants did not receive a hepatitis-b vaccination (HepB) at birth (or within the first 28 days of life). The 718 study participants that had 12.5 micrograms of mercury exposure within the first 28 days had received a single HepB at birth or soon after. The 10 subjects that had 25 micrograms of neonatal exposure had received a HepB at birth, or within one day of birth, and had received a second dose around age 27 or 28 days. The second dose was an early administration of HepB that typically would have been received after turning one or two months of age. The seven children that had 37.5 micrograms of neonatal exposure had received a hepatitis-b immune globulin and a hepatitis-B vaccine at birth, or within a day or two of birth.

Exhibit 9.1.1.4 is a graphical depiction of the postnatal exposure distributions that shows that there was considerable variation in cumulative exposures for the age ranges spanning 29-214 days, both for children who received a birth dose of hepatitis-b vaccine and for those who did not. Exhibit 9.1.1.5 shows the variation in frequency distributions across the four HMOs.

In 1999, children that were vaccinated on time and according to the recommended childhood immunization schedule[13] may have been exposed to 187.5 micrograms of ethylmercury from thimerosal during the age range spanning birth and seven months. This amount could have been achieved if the child received HepB vaccinations (12.5 μg) at birth, between the ages of 1 and 4 months, and at age 6 months, and received DTaP and Hib vaccinations (each with as much 25 μg of ethylmercury per dose) at ages 2, 4, and 6 months.

[13] The vaccine schedule recommended and approved by the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP).

There are several possible sources of variation among children in exposure amounts. The first is variation in vaccination policies among health care providers. For example, at some hospitals, HepB vaccinations were given to new-borns as a matter of policy, others did not have that policy. And some health care providers typically did not administer a Hib vaccine at age 6 months. Another source of variation is the mercury amounts contained within one dose of a vaccine. For example, depending on the manufacturer, Hib vaccines in use at that time contained 0, 12.5, or 25 μg of ethylmercury per dose. Another source of variation was the use of combined DTaP-Hib vaccines. The combined vaccine contained 25 μg of ethylmercury per dose. Receipt of separate DTaP and Hib vaccines at one visit could result exposure to 50 μg of ethylmercury. And finally, there was variation in exposure due to delayed or skipped vaccinations. Recommended vaccines were skipped or delayed due to personal circumstances, beliefs, and preferences. A total of 16 study participants were not vaccinated at all during the age range spanning birth to 7 months.

Exhibit 9.1.1.6 shows a schematic of the pattern of receipts that would result in 187.5 micrograms of cumulative exposure to ethylmercury. The exhibit also shows the modal (most frequently occurring) pattern of receipts of thimerosal-containing vaccines during the age range from birth to 7 months at each HMO. See Section 7.2 for additional information on vaccine types and exposure amounts.

One hundred eleven (11 percent) of the 1,047 study participants had prenatal exposure to ethylmercury from thimerosal-containing vaccines or immune globulins administered to their mothers during pregnancy. See Section 7.2 for additional details.

Exhibit 9.1.1.7 shows the intercorrelation among the variables measuring amounts of cumulative exposure in each age range. It shows that there are weak positive correlations between prenatal exposure and postnatal receipts of thimerosal-containing vaccines and immune globulins. Children that were exposed at birth (within the first 28 days) were slightly more likely to have higher exposure during the age range from 29 days to 7 months, as indicated by the weak positive correlation among the *Amt01mos* and *Amt17mos* variables. Since the *Amt07mos* variable is equal to the sum of the *Amt01mos* and *Amt17mos* variables, it is positively correlated to both.

Exhibit 9.1.1.3
Descriptive Statistics for Exposure Amounts

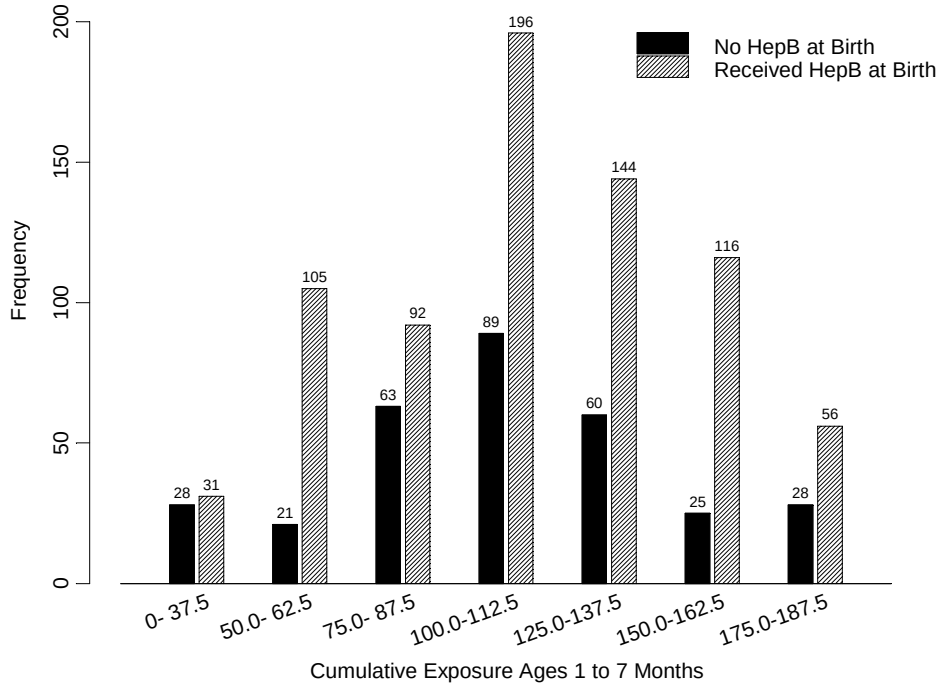
Cumulative Exposure Birth to 7 Months		**Cumulative Exposure Birth to 1 Month Crossed with Cumulative Exposure 1 to 7 Months**					
			Birth to 1 Month (0-28 Days)				
Birth to 7 Months (1-214 Days)	Total	1 to 7 Months (29-214 Days)	0 μg	12.5 μg	25 μg	37.5 μg	Total
0 μg	16	0 μg	16	3	0	0	19
12.5 μg	3	12.5 μg	0	0	0	0	0
25 μg	2	25 μg	2	2	1	0	5
37.5 μg	12	37.5 μg	10	24	0	0	34
50 μg	37	50 μg	12	14	1	0	27
62.5 μg	23	62.5 μg	9	89	0	0	98
75 μg	146	75 μg	56	20	1	0	77
87.5 μg	27	87.5 μg	7	69	1	0	77
100 μg	116	100 μg	46	121	1	2	170
112.5 μg	164	112.5 μg	42	70	0	2	114
125 μg	115	125 μg	44	105	0	3	152
137.5 μg	123	137.5 μg	16	35	0	0	51
150 μg	52	150 μg	15	7	5	0	27
162.5 μg	19	162.5 μg	9	103	0	0	112
175 μg	130	175 μg	22	56	0	0	78
187.5 μg	62	187.5 μg	6	0	0	0	6
Total	1047	Total	312	718	10	7	1047

μg = micrograms of ethylmercury from thimerosal in vaccines or immune globulins

Read table: Sixteen of the 1,047 study participants were exposed to 0 μg in the age range from birth to one month, and 0 μg in the age range spanning one to seven months.

Exhibit 9.1.1.4.
Frequency Distribution of Neonatal Exposure by Exposures 1-7 Months

Frequency Counts of Cumulative Exposure for Age Range of 1 to 7 Months Crossed with Exposure from Birth Dose of Hepatitis-B Vaccine



Read: "The study included 28 children who did not received a hepatitis-B vaccination in first month of life, and whose cumulative exposure to ethylmercury from vaccines during the age range from one to seven months was in the range of 0 to 37.5 micrograms."

Exhibit 9.1.1.5
Size of Analysis Sample from Each HMO by Exposure Category

	HMO-A		HMO-B		HMO-C		HMO-D		Total	
VSD Exposures	**HepB at Birth**		**HepB at Birth**		**HepB at Birth**		**HepB at Birth**		**HepB at Birth**	
Cumulative 1-7 Months	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
(0 to 62.5 μg)	26	49	11	69	10	10	2	6	49	134
(75.0 to 87.5 μg)	47	51	15	38	0	2	1	0	63	91
(100.0 to 112.5 μg)	44	55	40	94	3	36	1	11	88	196
(125.0 to 137.5 μg)	25	20	28	113	6	7	1	3	60	143
(150.0 to 162.5 μg)	7	7	2	3	8	74	7	31	24	115
(175.0 to 187.5 μg)	9	0	0	0	16	40	3	16	28	56
Total	158	182	96	317	43	169	15	67	312	735
	340		413		212		82		1047	

Note: μg = micrograms.

Exhibit 9.1.1.6.
Pattern of Receipts of Thimerosal-containing Vaccines Resulting in Maximum Cumulative Exposure Birth to 7 Months
and
Modal Patterns of Receipts at Each HMO

Age	Vaccine	Pattern Resulting in Maximum Cumulative Exposure	Modal Patterns at each HMO			
			HMO-A	HMO-B	HMO-C	HMO-D
Birth	HepB	12.5	12.5	12.5	12.5	12.5
1-4 months	HepB	12.5	12.5	12.5	12.5	12.5
6-7 months	HepB	12.5	12.5	12.5	.	.
2 months	DTaP	25	.	25	25	25
2 months	Hib	25	.	12.5	25	25
2months	DtaP-Hib	.	25	.	.	.
4 months	DtaP	25	.	25	25	25
4 months	Hib	25	.	12.5	25	25
4 months	DtaP-Hib	.	25	.	.	.
6 months	DtaP	25	.	25	25	25
6 months	Hib	25	.	.	25	25
6 months	DtaP-Hib	.	25	.	.	.
Cumulative Exposure Birth to 7 months:		187.5	112.5	137.5	175	175

Note: Ball et al (2001) estimated that a thimerosal-containing influenza vaccine that would have been recommended for children in selected populations could have been added to the maximum pattern shown above, resulting in 200 micrograms of cumulative exposure. In the current study, while there were four children that received the influenza vaccine before age seven months, none of these children had received all of the vaccinations in the pattern resulting in maximum exposure, depicted above. It is also conceptually possible for a child to have received more than 187.5 micrograms of cumulative exposure in the first seven months if the child had received a hepatitis-b immune globulin, in addition to all the vaccines depicted in the maximum pattern. That scenario, however, did not occur in the sample of children analyzed in the current study.

Exhibit 9.1.1.7. Correlation Among Exposure Amount Variables

	PreNat Thimer	Amt01mos	Amt17mos
PreNatThimer Cumulative μg : Prenatal	1		
Amount 0-1 mos Cumulative μg : birth-28 days	0.05 (0.137)	1	
Amt17mos Cumulative μg : 29-214 days	0.09 (0.003)	0.09 (0.003)	1
Amt07mos Cumulative μg : birth-214 days	0.10 (0.002)	0.24 (<0.001)	0.99 (<0.001)

Pearson Correlation Coefficients, N = 1047

9.1.2. Descriptive Statistics on Variables Used in Analysis Models

The means, standard deviations, minimums and maximums of the variables used in the analytical models are displayed in Exhibits 9.1.2.1 - 9.1.2.3. The correlations among the exposure variables that were used in the analytical models are shown in Exhibit 9.1.2.4, and the correlation among outcome variables is shown in Exhibit 9.1.2.5.

Exhibit 9.1.2.1. Descriptive Statistics on Outcome Measures

Test	Form of Score	N	Miss.	Mean	Std	Min	Max
Speech and Language							
Boston Naming Test	Raw score	1045	2	39.55	7.97	14	58
NEPSY: Speeded Naming	Raw score	1040	7	27.39	8.12	1	42
NEPSY: Comprehension of Instructions	Raw score	1034	13	23.58	2.82	12	28
CELF: Formulated Sentences	Raw score	1038	9	32.76	6.7	0	44
CELF: Recalling Sentences	Raw score	1044	3	44.59	14.32	5	78
GFTA: Articulation (lower = better)	Raw score	1025	22	1.57	1.88	0	18
Stuttering: Assessor Rating (lower = better)	0=None/very mild; 1=mild/severe	1043	4	0.03	0.18	0	1
Stuttering: Parent Rating (lower = better)	0=None/very mild; 1=mild/severe	1035	12	0.02	0.15	0	1
Stuttering: Teacher Rating (lower = better)	0=None/very mild; 1=mild/severe	728	319	0.09	0.29	0	1
Verbal Memory							
CVLT-C: Free Recall, No Delay	Raw score	1046	1	46.51	9.69	0	71
CVLT-C: Free Recall, Short Delay	Raw score	1047	0	9.73	2.72	0	15
CVLT-C: Cued Recall, Short Delay	Raw score	1045	2	10.3	2.4	1	15
CVLT-C: Free Recall, Long Delay	Raw score	1044	3	10.38	2.53	0	15
CVLT-C: Cued Recall, Long Delay	Raw score	1043	4	10.65	2.46	1	15
CMS Stories 1: Immediate Recall	Raw score	1038	9	47.36	15.5	0	77
CMS Stories 2: Delayed Recall	Raw score	1037	10	44.49	15.09	0	76
Achievement							
WJIII: Letter- Word Identification	Raw score	1043	4	50.9	9.38	16	73
Fine Motor Coordinatioin							
Grooved Pegboard: Dominant Hand (lower =	Time to completion (minutes)	1045	2	65.88	27.54	21	300
Grooved Pegboard: Non-dom Hand (lower = better)	Time to completion (minutes)	1039	8	73.69	31.72	20	300
Finger Tapping: Dominant Hand	Number of taps	1037	10	38.81	6.8	15.6	107
Finger Tapping: Non-dominant Hand	Number of taps	1034	13	34.47	6.25	15	86
Visual Spatial Ability							
Stanford Binet: Copying	Raw score	1038	9	18.2	3	3	28
Attention/Executive Functioning							
GDS Vigilance Task: Correct Responses	Raw score (# correct)	1042	5	40.47	5.13	0	45
GDS Vigilance Task: Errors (lower = better)	Raw score (# errors)	1042	5	7.55	13.31	0	162
WISC III: Digit Span, Forward Recall	Raw score	1045	2	8.06	1.88	3	15
WISC III: Digit Span, Backward Recall	Raw score	1046	1	4.53	1.64	0	13
WISC III: Digit Span, Combined	Raw score	1045	2	12.58	2.94	4	26
BRIEF Parent Rating: Metacognition (lower =	Raw score	1042	5	74.28	18.1	44	128
BRIEF Teacher Rating: Metacognition (lower =	Raw score	782	265	67.31	22.5	44	129
Behavior Regulation (lower = better)							
CRS-R: Parent Rating: Hyperactive/Impulsive	Raw score (# reported problems)	1041	6	5.42	5.1	0	25
CRS-R: Teacher Rating: Hyperactive/Impulsive	Raw score (# reported problems)	777	270	3.94	5.75	0	27
CRS-R: Parent Rating: Inattentive	Raw score (# reported problems)	1041	6	6.3	5.94	0	26
CRS-R: Teacher Rating: Inattentive	Raw score (# reported problems)	777	270	6.68	7.33	0	28
BRIEF Parent Rating: Behavior Regulation	Raw score (# reported problems)	1042	5	42.28	10.79	26	82
BRIEF Teacher Rating: Behavior Regulation	Raw score (# reported problems)	782	265	38.79	12	29	87
Tics (lower = better)							
Motor tics (current): Assessor Rating	0=None; 1=Any	1044	3	0.09	0.28	0	1
Phonics tics (current): Assessor Rating	0=None; 1=Any	1044	3	0.07	0.26	0	1
Motor tics (current): Parent Rating	0=None; 1=Any	1035	12	0.09	0.29	0	1
Phonics tics (current): Parent Rating	0=None; 1=Any	1037	10	0.1	0.3	0	1

Exhibit 9.1.2.1. Descriptive Statistics on Outcome Measures

Test	Form of Score	N	Miss.	Mean	Std	Min	Max
General Intellectual Functioning							
WASI Verbal IQ	Standardized score	1032	15	107.39	14.6	62	153
WASI Performance IQ	Standardized score	1038	9	105.06	15.27	67	147
WASI Full Scale IQ	Standardized score	1025	22	107.1	14.56	71	153

Exhibit 9.1.2.2 Descriptive Statistics on Exposure Variables

Variable	Description	N	Miss.	Mean	Std.	Min.	Max.
Variables Used in Primary Models							
PreNatThimer	Total prenatal mercury from thimerosal	1047	0	2.2	8.3	0	100
Exp07mos	Amt/Wt(KGs) birth-214 days	1047	0	19.8	7.1	0	38.3
HepB	Amt/Wt(KGs) birth-28 days	1047	0	2.6	1.8	0	12.7
Exp17mos	Amt/Wt(KGs) 29-214 days	1047	0	17.2	6.6	0	33.8
Variables Used in Models to Assess Influence of High Leverage Observations on Results							
PreNatThimer_Alt	Alternative Tot prenat (for sensitivity analysis)	1047	0	5.2	16.7	0	100
PN_Trunc	if PreNatThimer>25 then PN_Trunc=25	1047	0	1.8	5.6	0	25
HepBYN	1 if any HepB, 0 else	1047	0	0.7	0.5	0	1
Variable Used in Model for Multiple Sources of Prenatal Mercury Exposure							
PreNatAllMerc	Prenatal mercury from any source	1047	0	1.8	0.9	0	5
Variables Used in Concurrent Antibiotics-by-Exposure Interaction Models							
AbDays	# days child on antibiotics in period 1-214 days	1047	0	8.7	17.7	0	214
AbDays1_28	# days child on antibiotics in period 1-28 days	1047	0	0.4	2.1	0	28
AbDays29_214	# days child on antibiotics in period 29-214 days	1047	0	8.2	17	0	186
AbExp07mos	Exposure concurrent w/ antibiotics (ages 1-214 days)	1047	0	2.3	4.3	0	32.9
AbHepB	Exposure concurrent w/ antibiotics (ages 1-28 days)	1047	0	0.1	0.6	0	4.3
AbExp17mos	Exposure concurrent w/ antibiotics (ages 29-214 days)	1047	0	2.2	4.2	0	32.9

Exhibit 9.1.2.3. Descriptive Statistics on Covariates

Variable	Label	N	Imp[a]	Mean	Std	Min	Max
Variables Included in Every Model							
ChildAge	Child Age (Yrs) at assessment	1047	0	9.28	1.08	7.07	11
sexmale	Sex of child 0=female, 1=male	1047	0	0.49	0.50	0	1
Birth weight	Birth weight 2500-2999 grams	1047	0	0.11	0.32	0	1
	Birth weight 3000-3999 grams	1047	0	0.73	0.44	0	1
	Birth weight 4000+ grams	1047	0	0.15	0.36	0	1
Maternal IQ	Maternal IQ: Lower third of Distbn	1047	0	0.34	0.48	0	1
	Maternal IQ: Midd. third of Distbn	1047	0	0.30	0.46	0	1
	Maternal IQ: Upper third of Distbn	1047	23	0.35	0.48	0	1
HOME_TotalIndex	"HOME" Total Index	1047	0	11.98	1.95	3	16
PctPoverty1	(Percent of poverty line)/100	1047	15	4.12	2.60	0.2	22.7
Maternal Education	Mother EduH: No HS degree	1047	0	0.04	0.21	0	1
	Mother EduH: HS /GED	1047	0	0.16	0.36	0	1
	Mother EduH: Some College	1047	0	0.28	0.45	0	1
	Mother EduH: College degree	1047	0	0.51	0.50	0	1
SingleParent	Child lives in a single parent household(0/1)	1047	0	0.19	0.40	0	1
Site	=1 if HMO-A	1047	0	0.32	0.47	0	1
	=1 if HMO-B	1047	0	0.39	0.49	0	1
	=1 if HMO-C	1047	0	0.20	0.40	0	1
	=1 if HMO-D	1047	0	0.08	0.27	0	1
Child and Family Characteristics							
Computer Experience	Computer Experience = None	1047	1	0.01	0.10	0	1
	Computer Experience = Some	1047	1	0.41	0.49	0	1
	Computer Experience = Much	1047	1	0.58	0.49	0	1
Maternal Age	Maternal Age at Ch Birth: <=16 years	1047	0	0.00	0.05	0	1
	Maternal Age at Ch Birth: 17-39 years	1047	0	0.93	0.26	0	1
	Maternal Age at Ch Birth: >=40 years	1047	0	0.07	0.26	0	1
OlderSibs	Child has an older sibling (0/1)	1047	0	0.64	0.48	0	1
YoungerSibs	Child has a younger sibling (0/1)	1047	0	0.41	0.49	0	1
DayCareCentr	# of center-based day care settings prior to KG	1047	4	0.81	1.02	0	9
DayCareHome	# of home-based day care settings prior to KG	1047	4	1.48	1.44	0	14
EngOnly	English only at home	1047	0	0.63	0.48	0	1
Breast Feeding	Breast Fed: <1mo	1047	0	0.22	0.41	0	1
(Duration)	Breast Fed: 1-6mos	1047	0	0.37	0.48	0	1
	Breast Fed: 6+ mos	1047	0	0.42	0.49	0	1
Child Birth Conditions							
cMedicalHist_1	=1 if birth headCM +/- 2SD from Mean	1047	0	0.02	0.15	0	1
C5APGARImpVal1	5-minute apgar	1047	75	8.93	0.49	4	10
Prenatal Exposures (non-vaccine related)							
PreNatNicotine_1	Used tobacco during pregnancy	1047	2	0.08	0.26	0	1
PreNatAlcohol_1	0=never - 4 heavy	1047	4	0.09	0.37	0	4
Tuna Consumption	Prenatal Tuna: None	1047	55	0.31	0.46	0	1
	Prenatal Tuna: Moderate	1047	55	0.65	0.48	0	1
	Prenatal Tuna: High	1047	55	0.04	0.20	0	1
PreNatFish_1	1=Tuna, Ocean and Home Caught	1047	47	0.07	0.25	0	1

Exhibit 9.1.2.3. Descriptive Statistics on Covariates

Variable	Label	N	Imp[a]	Mean	Std	Min	Max
PreNatOrgMerc_1	# Merc containing contact lens, ear, eye, nasal	1047	34	0.11	0.46	0	4
PreNatHomePro_1	# Merc exp from therm, bulbs, switches etc.	1047	40	0.04	0.19	0	1
Tooth Amalgams	Amalgams: None	1047	39	0.19	0.39	0	1
PreNatFillings_1_L1	Amalgams: yes	1047	39	0.11	0.31	0	1
PreNatFillings_1_L2	Amalgams: yes & work, grind, or gum	1047	39	0.71	0.46	0	1
PreNatlead_1	Prenat lead from occup or residential	1047	8	0.15	0.36	0	1
PreNatIllDrug	1=Cocaine or Narcotic	1047	0	0.01	0.10	0	1
Child Medical Conditions							
IronDef_1	Anemia or iron deficiency	1047	0	0.02	0.15	0	1
ADHDstimulant	ADHD stim in 12 hrs prior to assessment	1047	0	0.00	0.04	0	1
ChdPICA_1	Child Pica	1047	10	0.04	0.20	0	1
Maternal Diagnoses							
MatLangDel	Maternal Language Delay	1047	0	0.00	0.07	0	1
MatSpeechDel	Maternal speech delay	1047	0	0.01	0.10	0	1
MatSTUTTER	Maternal stuttering	1047	0	0.01	0.11	0	1
MatADHD	Maternal ADHD	1047	0	0.01	0.11	0	1
MatTIC	Maternal tics	1047	0	0.00	0.00	0	0
Quadratic and Cubic Forms							
ChildAge2	ChildAge^2 (squared)	1047	0	87.31	19.87	50.01	120.95
ChildAge3	ChildAge^3 (cubed)	1047	0	831.84	276.88	353.67	1330.25
PctPoverty1_2	(PctPoverty1/100)**2 (squared)	1047	15	23.75	42.27	0.04	515.12
PctPoverty1_3	(PctPoverty1/100)**3 (cubed)	1047	15	198.26	768.15	0.01	11691.4
HOME_TotalIndex2	HOME_TotalIndex**2 (squared)	1047	0	147.35	44.69	9	256
HOME_TotalIndex3	HOME_TotalIndex**3 (cubed)	1047	0	1851.88	800.69	27	4096
Variables Used Only in Models for Finger Tapping Outcomes[b]							
Spline9	=1 if *ChildAge* > 9.0; =0 Else	1047	0	0.60	0.49	0	1
ChildAge_Spline9	*Childage * Spline9*	1047	0	6.04	4.93	0	11
ChildAge2_Spline9	*Childage^2 * Spline9*	1047	0	60.82	50.25	0	120.95

[a] Numbers listed in "Imp" column show the number of missing values that were replaced with imputed values.
[b] Finger tapping tests for children aged 9 and above were slightly different than tests for younger children. Spline term allows for separate intercepts for children above and below 9 years. Spline*ChildAge and Spline*ChildAge2 terms allow for different age slopes for children above and below 9 years.

Exhibit 9.1.2.4. Correlation Among Exposure Variables

	PreNat Thimer	HepB	Exp17mos
PreNatThimer Total prenat merc from thimerosal	1		
HepB Amt/Wt(KGs) birth-28 days	0.04 (0.204)	1	
Exp17mos Amt/Wt(KGs) 29-214 days	0.08 (0.012)	0.13 (<0.001)	1
Exp07mos Amt/Wt(KGs) birth-214 days	0.08 (0.007)	0.38 (<0.001)	0.97 (<0.001)

Pearson Correlation Coefficients, N = 1047

Exhibit 9.1.2.5. Correlation Among Outcome Measures

	Boston Nam	NEPSY: SP	NEPSY: C.I.	CELF: F.S.	CELF: R.S.	GFTA	Stutter -A	Stutter - P	Stutter - T	CVLT: FND	CVLT: FSD	CV:T" CSD	CVLT: FLD	CVLT: CLD	CMS -1	C<S-2	WJ -LWID	Peg -Dom	Peg -ND	Tap - Dom	Tap - ND	SB Copy	GDS-Corr	GDS-Err	Digit - F	Digit - B	Digit - C	Meta -P	Meta- T	Hyper- P	Hyper -T	Inatt -P	Inatt - T	Behavior - P	Behavior - T	Motor Tics-A	Motor Tics P	Phon Tics-A	Phon Tics-P	Verbal IQ	Perf IQ	Full IQ
Speech and Language																																										
Boston Naming Test	1	.52	.58	.61	.65	-.31	-.04	-.09	-.02	.42	.34	.39	.35	.37	.6	.62	.64	.14	.15	.29	.28	.29	.32	-.22	.35	.34	.41	-.08	-.14	-.11	-.08	-.09	-.14	-.08	-.11	-.02	-.08	.00	-.1	.66	.48	.65
NEPSY: Speeded Naming	.52	1	.51	.48	.51	-.24	-.06	-.06	-.07	.49	.45	.47	.46	.46	.45	.46	.6	.11	.13	.3	.26	.31	.35	-.32	.31	.39	.42	-.28	-.34	-.22	-.19	-.29	-.31	-.2	-.24	-.04	-.06	.00	-.06	.41	.37	.44
NEPSY: Comprehension of Instructions	.58	.51	1	.52	.63	-.18	-.08	-.08	-.05	.41	.31	.35	.35	.37	.49	.48	.5	.07	.08	.18	.17	.22	.32	-.26	.39	.4	.47	-.15	-.25	-.15	-.08	-.18	-.24	-.14	-.14	-.06	-.03	-.06	-.1	.52	.48	.57
CELF: Formulated Sentences	.61	.48	.52	1	.63	-.26	-.11	-.06	-.04	.4	.31	.33	.31	.32	.53	.54	.6	.17	.18	.3	.28	.26	.34	-.28	.31	.34	.39	-.12	-.18	-.13	-.09	-.14	-.16	-.15	-.14	-.07	-.11	.01	-.11	.52	.35	.5
CELF: Recalling Sentences	.65	.51	.63	.63	1	-.21	-.03	-.04	-.05	.44	.3	.33	.32	.32	.56	.56	.57	.17	.18	.22	.24	.28	.3	-.25	.57	.42	.6	-.14	-.21	-.14	-.11	-.14	-.19	-.12	-.16	-.08	-.05	-.05	-.13	.6	.4	.57
GFTA: Articulation (lower = better)	-.31	-.24	-.18	-.26	-.21	1	-.03	.02	.12	-.18	-.14	-.19	-.16	-.16	-.24	-.23	-.24	-.1	-.08	-.1	-.12	-.14	-.16	.14	-.11	-.09	-.12	-.04	.03	-.01	.07	-.03	.04	.01	.05	.03	-.02	-.05	.04	-.19	-.13	-.18
Stuttering: Assessor Rating (lower = better)	-.04	-.06	-.08	-.11	-.03	-.03	1	.09	.14	-.03	-.02	-.03	-.07	-.04	-.04	-.05	-.09	.03	.03	.02	.03	-.01	-.08	.15	-.01	.01	.00	.04	.09	.02	.02	.00	.09	.06	.1	.24	.24	.00	.04	-.08	-.04	-.07
Stuttering: Parent Rating (lower = better)	-.09	-.06	-.08	-.06	-.04	.02	.09	1	.17	-.04	-.02	-.02	-.02	-.05	-.05	-.04	-.06	.11	.11	-.04	.00	-.14	-.07	.17	-.01	-.07	-.05	.08	.1	.03	.02	.06	.12	.03	.05	.04	.05	.13	.11	-.13	-.1	-.13
Stuttering: Teacher Rating (lower = better)	-.02	-.07	-.05	-.04	-.05	.12	.14	.17	1	-.06	-.05	-.04	-.08	-.05	-.04	-.02	-.01	.05	.13	-.01	-.04	-.1	-.05	.07	-.04	-.02	-.04	.07	.14	.00	.1	.07	.14	.06	.18	.09	.07	.02	.08	-.02	-.05	-.04
Verbal Memory																																									
CVLT-C: Free Recall, No Delay	.42	.49	.41	.4	.44	-.18	-.03	-.04	-.06	1	.67	.7	.69	.68	.46	.46	.46	.14	.17	.18	.18	.23	.31	-.25	.23	.29	.31	-.17	-.21	-.16	-.14	-.16	-.2	-.16	-.19	-.03	.01	-.01	-.07	.3	.25	.32
CVLT-C: Free Recall, Short Delay	.34	.45	.31	.31	.3	-.14	-.02	-.02	-.05	.67	1	.74	.8	.74	.41	.42	.41	.14	.16	.16	.16	.23	.25	-.27	.14	.28	.24	-.18	-.22	-.16	-.16	-.18	-.21	-.15	-.18	-.03	-.04	.00	-.02	.24	.21	.25
CVLT-C: Cued Recall, Short Delay	.39	.47	.35	.33	.33	-.19	-.03	-.02	-.04	.7	.74	1	.79	.87	.43	.44	.42	.13	.15	.15	.17	.29	.25	-.25	.13	.26	.23	-.15	-.21	-.13	-.12	-.17	-.2	-.12	-.16	-.01	.00	-.01	-.04	.28	.25	.3
CVLT-C: Free Recall, Long Delay	.35	.46	.35	.31	.32	-.16	-.07	-.02	-.08	.69	.8	.79	1	.82	.38	.4	.42	.13	.14	.17	.18	.27	.22	-.27	.16	.28	.26	-.17	-.25	-.13	-.16	-.16	-.25	-.14	-.2	-.05	-.02	.01	-.03	.26	.25	.29
CVLT-C: Cued Recall, Long Delay	.37	.46	.37	.32	.32	-.16	-.04	-.05	-.05	.68	.74	.87	.82	1	.43	.44	.41	.15	.16	.13	.15	.31	.24	-.28	.17	.27	.26	-.14	-.21	-.12	-.12	-.15	-.21	-.11	-.16	-.02	-.04	-.01	-.03	.27	.27	.31
CMS Stories 1: Immediate Recall	.6	.45	.49	.53	.56	-.24	-.04	-.05	-.04	.46	.41	.43	.38	.43	1	.96	.55	.52	.52	.32	.32	.22	.28	-.16	.24	.3	.32	.01	-.09	-.05	-.05	-.02	-.07	-.03	-.07	-.07	-.03	.00	-.06	.36	.26	.36
CMS Stories 2: Delayed Recall	.62	.46	.48	.54	.56	-.23	-.05	-.04	-.02	.46	.42	.44	.4	.44	.96	1	.56	.5	.5	.3	.31	.22	.29	-.19	.24	.31	.33	.00	-.09	-.06	-.05	-.04	-.08	-.05	-.07	-.07	-.04	.01	-.05	.38	.27	.37
Achievement																																									
WJIII: Letter- Word Identification	.64	.6	.5	.6	.57	-.24	-.09	-.06	-.01	.46	.41	.42	.42	.41	.55	.56	1	.29	.31	.38	.39	.34	.39	-.24	.35	.44	.47	-.2	-.26	-.19	-.16	-.17	-.25	-.19	-.19	-.02	-.05	.03	-.09	.47	.37	.48
Fine Motor Coordination																																									
Grooved Pegboard:	.14	.11	.07	.17	.17	-.1	.03	.11	.05	.14	.14	.13	.13	.15	.52	.5	.29	1	.9	.21	.25	.05	.09	.02	.04	.07	.06	.16	.08	.04	-.01	.15	.1	.07	-.01	-.04	.05	.00	.01	-.13	-.18	-.18

Exhibit 9.1.2.5. Correlation Among Outcome Measures

	Boston Nam	NEPSY: SP	NEPSY: C.I.	CELF: F.S.	CELF: R.S.	GFTA	Stutter -A	Stutter - P	Stutter - T	CVLT: FND	CVLT: FSD	CV:T" CSD	CVLT: FLD	CVLT: CLD	CMS -1	C<S-2	WJ -LWID	Peg -Dom	Peg -ND	Tap - Dom	Tap - ND	SB Copy	GDS-Corr	GDS-Err	Digit - F	Digit - B	Digit - C	Meta -P	Meta- T	Hyper- P	Hyper -T	Inatt -P	Inatt - T	Behavior - P	Behavior - T	Motor Tics-A	Motor Tics P	Phon Tics-A	Phon Tics-P	Verbal IQ	Perf IQ	Full IQ
Dominant Hand (lower = better)																																									
Grooved Pegboard: Non-dom Hand (lower = better)	.15	.13	.08	.18	.18	-.08	.03	.11	.13	.17	.16	.15	.14	.16	.52	.5	.31	.9	1	.2	.21	.03	.08	.03	.05	.05	.06	.14	.07	.03	-.02	.15	.1	.06	.01	-.03	.05	.02	.01	-.1	-.18	-.16
Finger Tapping: Dominant Hand	.29	.3	.18	.3	.22	-.1	.02	-.04	-.01	.18	.16	.15	.17	.13	.32	.3	.38	.21	.2	1	.81	.22	.23	-.08	.14	.23	.22	-.02	-.01	-.01	.07	-.02	.00	-.05	.03	-.05	-.03	.07	.04	.07	.15	.13
Finger Tapping: Non-dominant Hand	.28	.26	.17	.28	.24	-.12	.03	.00	-.04	.18	.16	.17	.18	.15	.32	.31	.39	.25	.21	.81	1	.24	.2	-.06	.15	.2	.21	.00	.05	.00	.11	.00	.06	-.02	.06	-.03	.00	.07	.03	.07	.14	.13
Visual Spatial Ability																																									
Stanford Binet: Copying	.29	.31	.22	.26	.28	-.14	-.01	-.14	-.1	.23	.23	.29	.27	.31	.22	.22	.34	.05	.03	.22	.24	1	.23	-.22	.19	.24	.26	-.2	-.24	-.17	-.17	-.17	-.22	-.15	-.2	-.03	-.01	.02	-.02	.21	.34	.31
Attention/ Executive Functioning																																									
GDS Vigilance Task: Correct Responses	.32	.35	.32	.34	.3	-.16	-.08	-.07	-.05	.31	.25	.25	.22	.24	.28	.29	.39	.09	.08	.23	.2	.23	1	-.41	.18	.25	.26	-.17	-.17	-.15	-.09	-.14	-.16	-.17	-.11	-.06	-.03	.02	-.02	.22	.2	.24
GDS Vigilance Task: Errors (lower = better)	-.22	-.32	-.26	-.28	-.25	.14	.15	.17	.07	-.25	-.27	-.25	-.27	-.28	-.16	-.19	-.24	.02	.03	-.08	-.06	-.22	-.41	1	-.15	-.22	-.22	.24	.23	.19	.14	.26	.24	.18	.2	.05	.04	.07	.07	-.24	-.22	-.26
WISC III: Digit Span, Forward Recall	.35	.31	.39	.31	.57	-.11	-.01	-.01	-.04	.23	.14	.13	.16	.17	.24	.24	.35	.04	.05	.14	.15	.19	.18	-.15	1	.38	.86	-.1	-.15	-.1	-.06	-.12	-.15	-.08	-.1	-.08	-.07	-.08	-.1	.34	.31	.38
WISC III: Digit Span, Backward Recall	.34	.39	.4	.34	.42	-.09	.01	-.07	-.02	.29	.28	.26	.28	.27	.3	.31	.44	.07	.05	.23	.2	.24	.25	-.22	.38	1	.8	-.19	-.25	-.16	-.12	-.2	-.25	-.11	-.18	-.06	-.02	-.08	-.05	.29	.34	.36
WISC III: Digit Span, Combined	.41	.42	.47	.39	.6	-.12	.00	-.05	-.04	.31	.24	.23	.26	.26	.32	.33	.47	.06	.06	.22	.21	.26	.26	-.22	.86	.8	1	-.17	-.24	-.15	-.11	-.18	-.24	-.11	-.17	-.09	-.06	-.1	-.09	.38	.39	.44
BRIEF Parent Rating: Metacognition (lower = better)	-.08	-.28	-.15	-.12	-.14	-.04	.04	.08	.07	-.17	-.18	-.15	-.17	-.14	.01	.00	-.2	.16	.14	-.02	.00	-.2	-.17	.24	-.1	-.19	-.17	1	.57	.63	.35	.88	.54	.7	.39	.04	.01	.17	.18	-.18	-.17	-.2
BRIEF Teacher Rating: Metacognition (lower = better)	-.14	-.34	-.25	-.18	-.21	.03	.09	.1	.14	-.21	-.22	-.21	-.25	-.21	-.09	-.09	-.26	.08	.07	-.01	.05	-.24	-.17	.23	-.15	-.25	-.24	.57	1	.44	.67	.6	.93	.38	.74	.06	.07	.11	.13	-.23	-.18	-.23
Behavior Regulation (lower = better)																																									
CRS-R: Parent Rating: Hyperactive/Impulsive	-.11	-.22	-.15	-.13	-.14	-.01	.02	.03	.00	-.16	-.16	-.13	-.13	-.12	-.05	-.06	-.19	.04	.03	-.01	.00	-.17	-.15	.19	-.1	-.16	-.15	.63	.44	1	.45	.67	.41	.75	.45	.07	.06	.15	.17	-.15	-.14	-.17
CRS-R: Teacher Rating: Hyperactive/Impulsive	-.08	-.19	-.08	-.09	-.11	.07	.02	.02	.1	-.14	-.16	-.12	-.16	-.12	-.05	-.05	-.16	-.01	-.02	.07	.11	-.17	-.09	.14	-.06	-.12	-.11	.35	.67	.45	1	.37	.63	.34	.8	.01	.08	.03	.09	-.12	-.04	-.09
CRS-R: Parent Rating: Inattentive	-.09	-.29	-.18	-.14	-.14	-.03	.00	.06	.07	-.16	-.18	-.17	-.16	-.15	-.02	-.04	-.17	.15	.15	-.02	.00	-.17	-.14	.26	-.12	-.2	-.18	.88	.6	.67	.37	1	.57	.61	.44	.05	.02	.19	.18	-.19	-.15	-.19
CRS-R: Teacher	-.14	-.31	-.24	-.16	-.19	.04	.09	.12	.14	-.2	-.21	-.2	-.25	-.21	-.07	-.08	-.25	.1	.1	.00	.06	-.22	-.16	.24	-.15	-.25	-.24	.54	.93	.41	.63	.57	1	.35	.65	.05	.05	.11	.11	-.24	-.18	-.24

Exhibit 9.1.2.5. Correlation Among Outcome Measures

	Boston Nam	NEPSY: SP	NEPSY: C.I.	CELF: F.S.	CELF: R.S.	GFTA	Stutter -A	Stutter - P	Stutter - T	CVLT: FND	CVLT: FSD	CV:T" CSD	CVLT: FLD	CVLT: CLD	CMS -1	C<S-2	WJ -LWID	Peg -Dom	Peg -ND	Tap - Dom	Tap - ND	SB Copy	GDS-Corr	GDS-Err	Digit - F	Digit - B	Digit - C	Meta -P	Meta- T	Hyper- P	Hyper -T	Inatt -P	Inatt - T	Behavior - P	Behavior - T	Motor Tics-A	Motor Tics P	Phon Tics-A	Phon Tics-P	Verbal IQ	Perf IQ	Full IQ
Rating: Inattentive BRIEF Parent Rating: Behavior Regulation	-.08	-.2	-.14	-.15	-.12	.01	.06	.03	.06	-.16	-.15	-.12	-.14	-.11	-.03	-.05	-.19	.07	.06	-.05	-.02	-.15	-.17	.18	-.08	-.11	-.11	.7	.38	.75	.34	.61	.35	1	.41	.08	.04	.14	.23	-.13	-.15	-.16
BRIEF Teacher Rating: Behavior Regulation	-.11	-.24	-.14	-.14	-.16	.05	.1	.05	.18	-.19	-.18	-.16	-.2	-.16	-.07	-.07	-.19	-.01	.01	.03	.06	-.2	-.11	.2	-.1	-.18	-.17	.39	.74	.45	.8	.44	.65	.41	1	.1	.07	.05	.12	-.13	-.09	-.13
Tics (lower = better)																																									
Motor tics (current): Assessor Rating	-.02	-.04	-.06	-.07	-.08	.03	.24	.04	.09	-.03	-.03	-.01	-.05	-.02	-.07	-.07	-.02	-.04	-.03	-.05	-.03	-.03	-.06	.05	-.08	-.06	-.09	.04	.06	.07	.01	.05	.05	.08	.1	1	.31	.18	.1	-.03	-.03	-.03
Phonics tics (current): Assessor Rating	-.08	-.06	-.03	-.11	-.05	-.02	.24	.05	.07	.01	-.04	.00	-.02	-.04	-.03	-.04	-.05	.05	.05	-.03	.00	-.01	-.03	.04	-.07	-.02	-.06	.01	.07	.06	.08	.02	.05	.04	.07	.31	1	.03	.13	-.08	-.03	-.07
Motor tics (current): Parent Rating	.00	.00	-.06	.01	-.05	-.05	.00	.13	.02	-.01	.00	-.01	.01	-.01	.00	.01	.03	.00	.02	.07	.07	.02	.02	.07	-.08	-.08	-.1	.17	.11	.15	.03	.19	.11	.14	.05	.18	.03	1	.43	-.06	-.02	-.05
Phonics tics (current): Parent Rating	-.1	-.06	-.1	-.11	-.13	.04	.04	.11	.08	-.07	-.02	-.04	-.03	-.03	-.06	-.05	-.09	.01	.01	.04	.03	-.02	-.02	.07	-.1	-.05	-.09	.18	.13	.17	.09	.18	.11	.23	.12	.1	.13	.43	1	-.13	-.08	-.12
General Intellectual Functioning																																									
WASI Verbal IQ	.66	.41	.52	.52	.6	-.19	-.08	-.13	-.02	.3	.24	.28	.26	.27	.36	.38	.47	-.13	-.1	.07	.07	.21	.22	-.24	.34	.29	.38	-.18	-.23	-.15	-.12	-.19	-.24	-.13	-.13	-.03	-.08	-.06	-.13	1	.53	.87
WASI Performance IQ	.48	.37	.48	.35	.4	-.13	-.04	-.1	-.05	.25	.21	.25	.25	.27	.26	.27	.37	-.18	-.18	.15	.14	.34	.2	-.22	.31	.34	.39	-.17	-.18	-.14	-.04	-.15	-.18	-.15	-.09	-.03	-.03	-.02	-.08	.53	1	.88
WASI Full Scale IQ	.65	.44	.57	.5	.57	-.18	-.07	-.13	-.04	.32	.25	.3	.29	.31	.36	.37	.48	-.18	-.16	.13	.13	.31	.24	-.26	.38	.36	.44	-.2	-.23	-.17	-.09	-.19	-.24	-.16	-.13	-.03	-.07	-.05	-.12	.87	.88	1

Pearson Correlation Coefficients

9.2. Model Results

9.2.1. Overview

The model results section introduces the factors that motivated fitting each model, provides specifications of the models and interpretation of parameter estimates, and provides summaries of results fit to the data from the n=1,047 assessed children. Section 9.2.2 is devoted to main effect models that estimate exposure effects on the combined population of males and females. This section includes results of several variants of data subsets or coding of particular variables. These variants are used to assess the sensitivity of results to particular assumptions, analysis methods, or inclusion or omission of particular observations. The results in this section are approximately equally balanced between findings where increased exposure is associated with better outcome measures and findings where increased exposure is associated with worse outcomes.

Section 9.2.3 focuses on sex-by-exposure interaction models. Estimates of exposure effects on females and males are presented, as well as results of tests of sex-by-exposure interaction effects.

Sections 9.2.4 and 9.2.5 are devoted to the question of whether prenatal exposure exacerbates the effects of postnatal exposure. The results do not provide evidence to support the hypothesis.

Section 9.2.6 concentrates on analyses to determine whether concurrent antibiotic receipt exacerbates the effects of postnatal exposure. The pattern of results suggests random scatter of small numbers of positive and negative effects.

9.2.2. Main Effect Models

9.2.2.1. Introduction

This section summarizes the results of two main effects models that were fit to each of the 42 outcome variables. These models are considered to be of primary importance as they directly address the study's primary research questions. The first of the two models produces two hypothesis tests. One is a test of the null hypothesis that prenatal exposure to ethylmercury from thimerosal in vaccines and immune globulins is unrelated to the outcome measure. The second is a test of the null hypothesis that cumulative exposure, over the age range spanning birth to seven months, to ethylmercury from thimerosal used in vaccines and immune globulins is unrelated to the outcome measure.

The second of the two models produces three hypothesis tests. One is a test of the null hypothesis that ethylmercury exposures from thimerosal used in vaccines and immune globulins received during the age range spanning birth to 28 days is unrelated to the outcome measure. The second test is of the null hypothesis that cumulative exposures spanning the age range from 29 days to seven months is unrelated to the outcome. And the third is a test of the null hypothesis that prenatal exposure is unrelated to the outcome. The hypothesis tests concerning prenatal exposures in models 1 and 2 produce almost identical results.

These two models were fit to a full data set with single imputation for missing values on covariates, to a full data set with multiple imputation for missing values on covariates, to a data set with an alternative coding for prenatal exposure, to several variants used to assess the sensitivity of results regarding ADHD outcomes to coding of outcomes or inclusion/omission of children who have taken medication for ADHD, and to a data set with a single outlier omitted. Details on each are provided subsequently.

9.2.2.2. Model Specifications

The notation and variables shown in the model specifications below are defined in Chapter 8. For tics and stuttering outcomes, logistic regression models that are analogous to the linear regression models specified below, were fit to the data.

Model (1) Specification: Main Effects of Prenatal, and Cumulative Exposures from Birth to 7 Months

$$Y = \beta_0 + \beta_1 preNatThimer + \beta_2 Exp07mos + \sum_j \alpha_j oe_j + \sum_k \alpha_{j+k} cf_k + \sum_l \alpha_{j+k+l} St_l + \varepsilon$$

$$H_0 : \beta_1 = 0 \quad vs \quad H_a : \beta_1 \neq 0$$

$$H_0 : \beta_2 = 0 \quad vs \quad H_a : \beta_2 \neq 0$$

Model (2) Specification: Main Effects of Prenatal, Hepatitis B at Birth, 1-7 Month Exposures

$$Y = \beta_0 + \beta_1 preNatThimer + \beta_2 HepB + \beta_3 Exp17mos + \sum_j \alpha_j oe_j + \sum_k \alpha_{j+k} cf_k + \sum_l \alpha_{j+k+l} St_l + \varepsilon$$

$$H_0 : \beta_1 = 0 \quad vs \quad H_a : \beta_1 \neq 0$$
$$H_0 : \beta_2 = 0 \quad vs \quad H_a : \beta_2 \neq 0$$
$$H_0 : \beta_3 = 0 \quad vs \quad H_a : \beta_3 \neq 0$$

9.2.2.3. Explanation of Model Results Summary Table

Results from Models (1) and (2) are summarized in Exhibit 9.2.1. Model (1) is summarized in the left side of the exhibit, and the summary for Model (2) appears on the right-hand side. For each model and each outcome variable, the exhibit shows the parameter estimate, standard error, p-value from the hypothesis test, and a standardized regression coefficient for each of the ethylmercury exposure variables. As indicated in the exhibit, for some values, a higher score (positive value for parameter estimate) indicates a better outcome, and for others a lower score (negative value for parameter estimate) indicates a more desirable outcome.

Statistically significant relationships (i.e., $p<0.05$) are highlighted with a box around the p-value, shading inside the box, and either a "+" or a "*" next to the p-value, depending on the direction of the relationship. When the relationship was such that higher mercury exposure was related to worse values on the outcome measure, the significant p-value was highlighted with a blue box and a "*" appears next to the value. When the relationship was such that higher mercury exposure was related to better values on the outcome measure, the significant p-value was highlighted with a red box and a "+" appears next to the value. P-values that were above the $p<0.05$ criterion, but below $p<0.10$ are also highlighted in the exhibit with red or blue boxes. While these relationships do not satisfy the study's criterion for statistical significance, we felt that highlighting these weaker effects would help illuminate any pattern of relationships in the results.

For outcomes analyzed using linear regression models (i.e., outcomes other than tics and stuttering), the values in the standardized regression coefficient column (labeled "StCf" in the exhibit) indicate the model predicted difference of the outcome measure, expressed in standard deviation units, associated with an increase of one standard deviation unit of the exposure measure. For example, in Exhibit 9.2.1, the standardized coefficient for the significant relationship of prenatal exposure to the NEPSY speeded naming outcome measure is 0.058. Therefore, the model predicts that an increase of one standard deviation unit of prenatal exposure is associated with improved scores on this outcome measure where the amount of improvement is equal to 0.058 standard deviation units of the outcome measure. Within the prenatal exposure column, it is reasonable to compare values of the standardized coefficients among all of the outcomes (except the tics and stuttering outcomes, which will be discussed subsequently). Therefore we may conclude that the size of the estimated beneficial effect of prenatal exposure on the NEPSY Speeded Naming outcome (0.058 standard deviation units), is similar to the size of the estimated harmful effect of prenatal exposure on the WISC III Digit Span Backward Recall outcome measure (-0.066 standard deviation units).

For each of the exposure measures, one can think of a difference of two standard deviation units as approximately corresponding to the difference between high and low exposure. Therefore, for the outcomes analyzed using linear regression models, doubling the standardized regression coefficient gives an effect size that roughly corresponds to the difference between high and low exposure. Returning to the NEPSY Speeded Naming example, one can think of the model predicted results as indicating that the difference between high and low prenatal exposure roughly corresponds to an effect size of 0.116.

For the tics and stuttering outcomes, which were analyzed in logistic regression models, the value in the standardized regression coefficient column corresponds to the odds ratio associated with an increase of two standard deviation units of the exposure measure. For example, in Exhibit 9.2.1, the value in the "SdCF" column of the "Exp07Mos" exposure variable for "Motor tics (current): Assessor Rating" is 1.357. That means that the estimated effect of a two standard deviation increase in cumulative exposures in the age range from birth to seven months, is a 36 percent increase in the likelihood of assessor reported motor tics. When increased exposure is related to a decrease in the probability of the outcome, the odds ratio takes a value less than one. An example from Model (2), corresponding to *HepB* exposure for parent reported motor tics, is a value in the "SdCF" column equal to 0.665. In order to get a sense of the relative magnitude of values that are less than one, as compared to values that are greater than one, the reader can invert the values. Inverting the value in this example gives 1/0.665 = 1.50. Thus the model predicted effect of a two standard deviation increase in *HepB* exposure, is a 50 percent increase in the likelihood of *not* having parent reported motor tics. This effect was not significantly different than zero.

For details on the calculation of the values in the StCF columns of the exhibit, see Chapter 8.

9.2.2.4. Results

9.2.2.4.1. Main Effect Models with Single Imputation for Covariates with Missing Values

Across the collection of outcome measures that were assessed in this study, the model results summarized in Exhibit 9.2.2.1 do not suggest clear evidence of either harm or benefit of increased exposure to ethylmercury from vaccines or immune globulins. The results indicate that increased mercury exposure was about as likely to be associated with better outcomes as it was to be associated with worse outcomes. Higher levels of prenatal exposure was related to worse scores on the WISC III Digit Span Backward Recall assessment, but was associated with better scores on the NEPSY Speeded Naming test. Cumulative exposures spanning the age range from birth to seven months was associated with better scores on the Grooved Pegboard test with the non-dominant hand, and with better scores on WISC III Digit Span Backward Recall assessment. Higher exposure in the first month of life (*HepB* exposure) was associated with more errors on the GFTA Test of Articulation, but with higher scores on the Finger Tapping test with the dominant hand. And finally, cumulative exposures during the age range spanning 1 to 7 months had no significant associations that were in the direction of worse outcomes, but was associated with better scores on the WJIII Letter Word Identification test, and better scores on the Grooved Pegboard test with the non-dominant hand.

Among the results that were highlighted because the p-values were above 0.05, but below 0.10, there was a similar pattern of approximate balance between findings where the association was in the direction of higher exposure being related to worse outcomes and associations that were in direction of higher exposure being related to better outcomes.

Exhibit 9.2.2.1 Main Effect Models (1) and (2) (n=1,047)

	Main Effects Model (1)								Main Effects Model (2)											
	PreNatThimer				Exp07mos				PreNatThimer				HepB				Exp17mos			
Test	Est	S.E.	P	StCf	Est	S.E.	P	StCf	Est	S.E.	P	StCf	Est	S.E.	P	StCf	Est	S.E.	P	StCf
Speech and Language																				
Boston Naming Test	0.032	0.022	0.143	0.033	0.050	0.030	0.096	0.045	0.032	0.022	0.133	0.034	-0.044	0.101	0.664	-0.011	0.061	0.032	0.058	0.051
NEPSY: Speeded Naming	0.057	0.027	0.034 +	0.058	0.010	0.038	0.784	0.009	0.058	0.027	0.033 +	0.059	-0.058	0.126	0.646	-0.014	0.019	0.041	0.650	0.015
NEPSY: Comprehension of Instructions	-0.002	0.010	0.860	-0.005	-0.014	0.014	0.310	-0.035	-0.002	0.010	0.873	-0.005	-0.030	0.045	0.504	-0.020	-0.012	0.015	0.412	-0.028
CELF: Formulated Sentences	0.021	0.021	0.327	0.026	-0.035	0.030	0.237	-0.038	0.021	0.021	0.319	0.026	-0.077	0.099	0.435	-0.022	-0.031	0.032	0.337	-0.030
CELF: Recalling Sentences	0.058	0.044	0.187	0.034	-0.001	0.062	0.984	-0.001	0.059	0.044	0.182	0.034	-0.079	0.206	0.703	-0.011	0.008	0.066	0.908	0.004
GFTA: Articulation (lower = better)	-0.002	0.007	0.804	-0.007	0.011	0.010	0.249	0.042	-0.002	0.007	0.735	-0.010	0.075	0.032	0.017 *	0.077	0.004	0.010	0.718	0.013
Stuttering: Assessor Rating (lower = better)	-0.002	0.021	0.907	0.959	0.026	0.033	0.434	1.443	-0.003	0.021	0.898	0.956	0.054	0.103	0.599	1.229	0.022	0.035	0.521	1.346
Stuttering: Parent Rating (lower = better)	-0.024	0.048	0.616	0.668	0.020	0.043	0.644	1.327	-0.024	0.049	0.620	0.667	-0.118	0.125	0.346	0.638	0.034	0.045	0.451	1.571
Stuttering: Teacher Rating (lower = better)	-0.042	0.030	0.160	0.500	0.011	0.025	0.674	1.163	-0.041	0.030	0.162	0.503	0.029	0.074	0.696	1.118	0.008	0.026	0.753	1.117
Verbal Memory																				
CVLT-C: Free Recall, No Delay	0.029	0.033	0.385	0.024	-0.001	0.046	0.975	-0.001	0.028	0.033	0.389	0.024	0.013	0.153	0.935	0.002	-0.003	0.049	0.950	-0.002
CVLT-C: Free Recall, Short Delay	-0.001	0.009	0.887	-0.004	-0.024	0.013	0.066	-0.063	-0.001	0.009	0.884	-0.004	-0.019	0.043	0.664	-0.013	-0.025	0.014	0.076	-0.060
CVLT-C: Cued Recall, Short Delay	-0.001	0.008	0.910	-0.003	-0.005	0.011	0.639	-0.016	-0.001	0.008	0.889	-0.004	0.026	0.038	0.497	0.020	-0.009	0.012	0.464	-0.025
CVLT-C: Free Recall, Long Delay	0.001	0.009	0.917	0.003	-0.019	0.012	0.108	-0.054	0.001	0.009	0.914	0.003	-0.023	0.040	0.562	-0.018	-0.019	0.013	0.139	-0.050
CVLT-C: Cued Recall, Long Delay	0.005	0.008	0.568	0.016	0.001	0.012	0.928	0.003	0.005	0.008	0.574	0.016	0.008	0.039	0.845	0.006	0.000	0.013	0.981	0.001
CMS Stories 1: Immediate Recall	0.024	0.042	0.570	0.013	-0.030	0.060	0.610	-0.014	0.024	0.042	0.563	0.013	-0.084	0.197	0.671	-0.010	-0.024	0.063	0.701	-0.010
CMS Stories 2: Delayed Recall	-0.010	0.041	0.817	-0.005	0.005	0.059	0.936	0.002	-0.009	0.041	0.828	-0.005	-0.066	0.193	0.732	-0.008	0.013	0.063	0.834	0.006
Achievement																				
WJIII: Letter- Word Identification	0.011	0.026	0.675	0.010	0.062	0.037	0.094	0.047	0.012	0.026	0.639	0.011	-0.089	0.122	0.469	-0.018	0.079	0.039	0.045 +	0.056
Fine Motor Coordination																				
Grooved Pegboard: Dominant Hand (lower = better)	-0.109	0.064	0.089	-0.033	-0.080	0.089	0.371	-0.021	-0.107	0.064	0.095	-0.032	-0.282	0.299	0.347	-0.020	-0.058	0.094	0.542	-0.014
Grooved Pegboard: Non-dom Hand (lower = better)	-0.083	0.077	0.284	-0.022	-0.274	0.109	0.012 +	-0.062	-0.083	0.077	0.282	-0.022	-0.226	0.362	0.532	-0.014	-0.279	0.116	0.017+	-0.059
Finger Tapping: Dominant Hand	-0.015	0.022	0.502	-0.018	0.034	0.031	0.271	0.036	-0.016	0.022	0.459	-0.020	0.222	0.103	0.032 +	0.062	0.013	0.033	0.705	0.012
Finger Tapping: Non-dominant Hand	-0.015	0.020	0.455	-0.020	0.018	0.028	0.524	0.020	-0.015	0.020	0.451	-0.020	0.039	0.093	0.676	0.012	0.016	0.030	0.605	0.017
Visual Spatial Ability																				
Stanford Binet: Copying	0.005	0.011	0.628	0.014	0.007	0.015	0.667	0.016	0.005	0.011	0.611	0.015	-0.022	0.050	0.662	-0.014	0.010	0.016	0.542	0.022
Attention/Executive Functioning																				
GDS Vigilance Task: Correct Responses	-0.013	0.018	0.470	-0.021	0.032	0.026	0.209	0.045	-0.013	0.018	0.485	-0.021	-0.009	0.085	0.914	-0.003	0.037	0.027	0.176	0.048
GDS Vigilance Task: Errors (lower = better)	0.033	0.047	0.489	0.020	-0.022	0.067	0.742	-0.012	0.032	0.047	0.493	0.020	0.000	0.220	0.999	0.000	-0.025	0.071	0.730	-0.012
WISC III: Digit Span, Forward Recall	0.000	0.007	0.983	0.001	-0.002	0.010	0.820	-0.008	0.000	0.007	0.965	0.001	-0.017	0.032	0.594	-0.017	0.000	0.010	0.964	-0.002
WISC III: Digit Span, Backward Recall	-0.013	0.006	0.027 *	-0.066	0.018	0.008	0.028 +	0.078	-0.013	0.006	0.025 *	-0.067	0.038	0.028	0.170	0.044	0.016	0.009	0.069	0.064
WISC III: Digit Span, Combined	-0.012	0.010	0.244	-0.034	0.017	0.015	0.242	0.041	-0.012	0.010	0.245	-0.034	0.014	0.048	0.773	0.009	0.017	0.015	0.262	0.039
BRIEF Parent Rating: Metacognition (lower = better)	0.021	0.066	0.744	0.010	-0.052	0.092	0.573	-0.020	0.021	0.066	0.750	0.010	0.009	0.307	0.976	0.001	-0.059	0.098	0.549	-0.022
BRIEF Teacher Rating: Metacognition (lower = better)	0.026	0.088	0.764	0.010	-0.147	0.133	0.268	-0.046	0.024	0.088	0.784	0.009	0.011	0.431	0.980	0.001	-0.165	0.140	0.241	-0.049
Behavior Regulation (lower = better)																				
CRS-R: Parent Rating: Hyperactive/Impulsive	0.007	0.019	0.725	0.011	0.019	0.026	0.469	0.026	0.006	0.019	0.745	0.010	0.071	0.087	0.414	0.027	0.013	0.028	0.641	0.017
CRS-R: Teacher Rating: Hyperactive/Impulsive	0.023	0.022	0.301	0.033	-0.048	0.034	0.157	-0.059	0.023	0.022	0.310	0.032	-0.016	0.110	0.883	-0.005	-0.051	0.036	0.150	-0.059
CRS-R: Parent Rating: Inattentive	0.011	0.022	0.606	0.016	-0.024	0.030	0.433	-0.028	0.011	0.022	0.619	0.015	0.019	0.100	0.848	0.006	-0.028	0.032	0.374	-0.032
CRS-R: Teacher Rating: Inattentive	0.002	0.029	0.939	0.002	-0.034	0.043	0.432	-0.033	0.002	0.029	0.957	0.002	0.014	0.141	0.919	0.004	-0.039	0.046	0.390	-0.036
BRIEF Parent Rating: Behavior Regulation	-0.021	0.040	0.594	-0.016	0.077	0.055	0.167	0.050	-0.020	0.040	0.616	-0.015	-0.069	0.185	0.711	-0.012	0.093	0.059	0.115	0.057
BRIEF Teacher Rating: Behavior Regulation	0.035	0.048	0.455	0.024	-0.045	0.072	0.535	-0.026	0.032	0.048	0.498	0.022	0.182	0.231	0.432	0.029	-0.071	0.076	0.353	-0.039
Tics (lower = better)																				
Motor tics (current): Assessor Rating	0.017	0.011	0.104	1.336	0.032	0.022	0.142	1.586	0.018	0.011	0.089	1.357	-0.026	0.068	0.696	0.904	0.039	0.023	0.094	1.680
Phonics tics (current): Assessor Rating	-0.011	0.018	0.560	0.839	0.037	0.023	0.102	1.702	-0.011	0.018	0.560	0.839	0.041	0.073	0.574	1.169	0.037	0.024	0.120	1.634
Motor tics (current): Parent Rating	0.003	0.012	0.832	1.043	-0.001	0.021	0.963	0.986	0.004	0.012	0.768	1.062	-0.107	0.069	0.122	0.665	0.012	0.022	0.599	1.167
Phonics tics (current): Parent Rating	-0.014	0.016	0.409	0.798	0.007	0.019	0.699	1.109	-0.014	0.016	0.401	0.795	0.028	0.064	0.666	1.112	0.005	0.020	0.803	1.068
General Intellectual Functioning																				
WASI Verbal IQ	0.054	0.047	0.252	0.030	-0.044	0.066	0.506	-0.021	0.057	0.047	0.224	0.032	-0.408	0.219	0.063	-0.053	-0.003	0.070	0.961	-0.002
WASI Performance IQ	-0.008	0.054	0.881	-0.004	0.130	0.074	0.080	0.061	-0.010	0.054	0.856	-0.005	0.323	0.252	0.200	0.040	0.110	0.079	0.162	0.048
WASI Full Scale IQ	0.026	0.048	0.594	0.015	0.059	0.068	0.383	0.029	0.027	0.048	0.575	0.015	-0.084	0.225	0.707	-0.011	0.075	0.072	0.295	0.034

Key: Mercury effect = Better Outcome — < .05 p-value+ — >.05, <.10 p-value

Mercury effect =Worse Outcome — < .05 p-value* — >.05, <.10 p-value

P-values shown are rounded to 3 decimal places. Therefore, a value shown as 0.050 may satisify p<0.05 criterion if the original value was rounded up, or may not satisify the criterion if the value was rounded down.

9.2.2.4.2. Main Effect Models With Multiple Imputation for Covariates with Missing Values

When covariates had missing values, the missing values were replaced with imputed values. The imputed values were the predicted values from regression models with random noise added. The amount of missing data on covariates is shown in Section 9.1.

For the models summarized in the previous section, and all other models except those summarized in the current section, a single imputed value replaced each missing value. In order to assess whether the model results were sensitive to the imputation, we the applied method of multiple imputation described in Little and Rubin (2002) to the two main effects models previously discussed. Briefly, the method of multiple imputation involves imputing ten separate values for each missing value. Each is a little different because of the random noise added to the predicted value from the regression. Ten separate data sets are created to accommodate the ten sets of imputations. Next, ten separate regression models are fit to the ten data sets. A parameter estimate from the multiple imputation method is the mean of the parameter estimates from the 10 separate models fit to the 10 separate data sets. The standard error of the coefficient is calculated as a function of the average of the standard errors from the 10 models, and the amount of between-imputation variation in parameter estimates.

We fit multiple imputation models for the two main effects models to the data from the 42 outcome variables. The results are summarized in Exhibit 9.2.2.2. There were no substantive difference between results from the multiple- and single-imputation methods.

It is not surprising that the multiple imputation results are very close to the single imputation results. The imputations were for covariates only, and most covariates had only small amounts of missing data.

Exhibit 9.2.2.2 Main Effect Models (1) and (2) with Multiple Imputation for Missing Values of Covariates (n=1,047)

	Main Effects Model (1)								Main Effects Model (2)											
	PreNatThimer				Exp07mos				PreNatThimer				HepB				Exp17mos			
Test	**Est**	**S.E.**	**P**	**StCf**	**Est**	**S.E.**	**P**	**StCf**	**Est**	**S.E.**	**P**	**StCf**	**Est**	**S.E.**	**P**	**StCf**	**Est**	**S.E.**	**P**	**StCf**
Speech and Language																				
Boston Naming Test	0.031	0.022	0.145	0.033	0.052	0.030	0.087	0.046	0.032	0.022	0.135	0.034	-0.040	0.101	0.695	-0.009	0.062	0.032	0.054	0.052
NEPSY: Speeded Naming	0.057	0.027	0.033+	0.059	0.011	0.038	0.771	0.010	0.058	0.027	0.032+	0.059	-0.053	0.126	0.674	-0.012	0.019	0.041	0.647	0.015
NEPSY: Comprehension of Instructions	-0.002	0.010	0.868	-0.005	-0.014	0.014	0.316	-0.035	-0.001	0.010	0.880	-0.004	-0.029	0.045	0.528	-0.019	-0.012	0.015	0.412	-0.028
CELF: Formulated Sentences	0.020	0.021	0.343	0.025	-0.035	0.030	0.244	-0.037	0.020	0.021	0.335	0.025	-0.076	0.099	0.440	-0.022	-0.030	0.032	0.344	-0.030
CELF: Recalling Sentences	0.057	0.044	0.194	0.033	0.002	0.062	0.979	0.001	0.058	0.044	0.189	0.034	-0.073	0.206	0.724	-0.010	0.010	0.066	0.877	0.005
GFTA: Articulation (lower = better)	-0.002	0.007	0.811	-0.007	0.011	0.010	0.255	0.041	-0.002	0.007	0.741	-0.010	0.075	0.032	0.018*	0.076	0.004	0.010	0.724	0.013
Stuttering: Assessor Rating (lower = better)	-0.002	0.021	0.907	0.959	0.026	0.033	0.434	1.443	-0.003	0.021	0.899	0.956	0.054	0.103	0.599	1.229	0.022	0.035	0.521	1.346
Stuttering: Parent Rating (lower = better)	-0.024	0.048	0.616	0.668	0.020	0.043	0.644	1.327	-0.024	0.049	0.620	0.667	-0.118	0.125	0.346	0.638	0.034	0.045	0.451	1.571
Stuttering: Teacher Rating (lower = better)	-0.042	0.030	0.160	0.500	0.011	0.025	0.674	1.163	-0.041	0.030	0.162	0.503	0.029	0.074	0.696	1.118	0.008	0.026	0.754	1.117
Verbal Memory																				
CVLT-C: Free Recall, No Delay	0.028	0.033	0.393	0.024	-0.001	0.046	0.982	-0.001	0.028	0.033	0.397	0.024	0.015	0.154	0.924	0.003	-0.003	0.049	0.954	-0.002
CVLT-C: Free Recall, Short Delay	-0.001	0.009	0.903	-0.003	-0.024	0.013	0.065	-0.063	-0.001	0.009	0.899	-0.004	-0.019	0.043	0.666	-0.013	-0.025	0.014	0.075	-0.060
CVLT-C: Cued Recall, Short Delay	-0.001	0.008	0.912	-0.003	-0.005	0.011	0.649	-0.015	-0.001	0.008	0.891	-0.004	0.026	0.038	0.491	0.021	-0.009	0.012	0.471	-0.024
CVLT-C: Free Recall, Long Delay	0.001	0.009	0.907	0.003	-0.019	0.012	0.109	-0.054	0.001	0.009	0.904	0.003	-0.023	0.040	0.570	-0.017	-0.019	0.013	0.139	-0.050
CVLT-C: Cued Recall, Long Delay	0.005	0.008	0.560	0.017	0.001	0.012	0.942	0.003	0.005	0.008	0.567	0.016	0.008	0.039	0.838	0.006	0.000	0.013	0.999	0.000
CMS Stories 1: Immediate Recall	0.024	0.042	0.573	0.013	-0.030	0.060	0.613	-0.014	0.024	0.042	0.566	0.013	-0.084	0.197	0.671	-0.010	-0.024	0.063	0.705	-0.010
CMS Stories 2: Delayed Recall	-0.010	0.041	0.805	-0.006	0.003	0.059	0.953	0.002	-0.010	0.041	0.816	-0.005	-0.066	0.194	0.734	-0.008	0.012	0.063	0.853	0.005
Achievement																				
WJIII: Letter- Word Identification	0.011	0.026	0.676	0.010	0.063	0.037	0.091	0.048	0.012	0.026	0.639	0.011	-0.089	0.123	0.470	-0.018	0.080	0.039	0.042+	0.057
Fine Motor Coordination																				
Grooved Pegboard: Dominant Hand (lower = better)	-0.109	0.064	0.089	-0.033	-0.081	0.089	0.362	-0.021	-0.107	0.064	0.095	-0.032	-0.298	0.299	0.319	-0.021	-0.057	0.094	0.544	-0.014
Grooved Pegboard: Non-dom Hand (lower = better)	-0.086	0.077	0.267	-0.023	-0.276	0.109	0.012+	-0.062	-0.086	0.077	0.266	-0.023	-0.241	0.362	0.507	-0.015	-0.281	0.117	0.016+	-0.059
Finger Tapping: Dominant Hand	-0.015	0.022	0.502	-0.018	0.035	0.031	0.255	0.037	-0.016	0.022	0.459	-0.020	0.224	0.103	0.030+	0.063	0.014	0.033	0.681	0.013
Finger Tapping: Non-dominant Hand	-0.014	0.020	0.490	-0.018	0.020	0.028	0.477	0.023	-0.014	0.020	0.484	-0.019	0.043	0.094	0.650	0.013	0.018	0.030	0.560	0.019
Visual Spatial Ability																				
Stanford Binet: Copying	0.005	0.011	0.610	0.015	0.006	0.015	0.686	0.015	0.006	0.011	0.593	0.016	-0.022	0.050	0.661	-0.014	0.009	0.016	0.561	0.021
Attention/Executive Functioning																				
GDS Vigilance Task: Correct Responses	-0.013	0.018	0.484	-0.021	0.034	0.026	0.188	0.047	-0.012	0.018	0.499	-0.020	-0.007	0.085	0.932	-0.003	0.039	0.027	0.158	0.050
GDS Vigilance Task: Errors (lower = better)	0.031	0.047	0.506	0.020	-0.024	0.067	0.717	-0.013	0.031	0.047	0.509	0.020	-0.005	0.220	0.981	-0.001	-0.026	0.071	0.711	-0.013
WISC III: Digit Span, Forward Recall	0.000	0.007	0.999	0.000	-0.002	0.010	0.852	-0.007	0.000	0.007	0.982	0.001	-0.016	0.032	0.607	-0.017	0.000	0.010	0.993	0.000
WISC III: Digit Span, Backward Recall	-0.013	0.006	0.028*	-0.065	0.018	0.008	0.027+	0.079	-0.013	0.006	0.027*	-0.066	0.038	0.028	0.169	0.044	0.016	0.009	0.066	0.065
WISC III: Digit Span, Combined	-0.012	0.010	0.243	-0.034	0.018	0.015	0.226	0.043	-0.012	0.010	0.244	-0.034	0.015	0.048	0.753	0.010	0.018	0.015	0.248	0.040
BRIEF Parent Rating: Metacognition (lower = better)	0.018	0.066	0.785	0.008	-0.050	0.092	0.584	-0.020	0.017	0.066	0.791	0.008	0.006	0.307	0.984	0.001	-0.057	0.098	0.562	-0.021
BRIEF Teacher Rating: Metacognition (lower = better)	0.026	0.088	0.766	0.010	-0.144	0.133	0.278	-0.045	0.024	0.088	0.787	0.009	0.018	0.431	0.966	0.002	-0.162	0.140	0.249	-0.048
Behavior Regulation (lower = better)																				
CRS-R: Parent Rating: Hyperactive/Impulsive	0.007	0.019	0.709	0.011	0.019	0.026	0.461	0.027	0.006	0.019	0.729	0.010	0.072	0.087	0.409	0.027	0.013	0.028	0.632	0.017
CRS-R: Teacher Rating: Hyperactive/Impulsive	0.023	0.022	0.307	0.033	-0.047	0.034	0.163	-0.058	0.022	0.022	0.317	0.032	-0.012	0.110	0.911	-0.004	-0.051	0.036	0.154	-0.059
CRS-R: Parent Rating: Inattentive	0.011	0.022	0.625	0.015	-0.023	0.030	0.443	-0.028	0.010	0.022	0.637	0.014	0.019	0.100	0.846	0.006	-0.028	0.032	0.383	-0.031
CRS-R: Teacher Rating: Inattentive	0.001	0.029	0.971	0.001	-0.034	0.043	0.432	-0.033	0.000	0.029	0.989	0.000	0.015	0.141	0.915	0.004	-0.040	0.046	0.389	-0.036
BRIEF Parent Rating: Behavior Regulation	-0.022	0.040	0.577	-0.017	0.077	0.055	0.166	0.050	-0.021	0.040	0.599	-0.016	-0.069	0.185	0.711	-0.012	0.093	0.059	0.114	0.057
BRIEF Teacher Rating: Behavior Regulation	0.038	0.047	0.421	0.026	-0.041	0.072	0.566	-0.024	0.035	0.048	0.463	0.024	0.189	0.231	0.414	0.030	-0.068	0.076	0.372	-0.038
Tics (lower = better)																				
Motor tics (current): Assessor Rating	0.017	0.011	0.104	1.336	0.032	0.022	0.142	1.586	0.018	0.011	0.089	1.357	-0.026	0.068	0.696	0.904	0.039	0.023	0.094	1.680
Phonics tics (current): Assessor Rating	-0.011	0.018	0.560	0.839	0.037	0.023	0.102	1.702	-0.011	0.018	0.560	0.839	0.041	0.073	0.575	1.169	0.037	0.024	0.120	1.634
Motor tics (current): Parent Rating	0.003	0.012	0.832	1.043	-0.001	0.021	0.963	0.986	0.004	0.012	0.768	1.062	-0.107	0.069	0.122	0.665	0.012	0.022	0.599	1.167
Phonics tics (current): Parent Rating	-0.014	0.016	0.409	0.798	0.007	0.019	0.699	1.109	-0.014	0.016	0.401	0.795	0.028	0.064	0.666	1.112	0.005	0.020	0.803	1.068
General Intellectual Functioning																				
WASI Verbal IQ	0.053	0.047	0.253	0.030	-0.039	0.066	0.557	-0.019	0.057	0.047	0.225	0.032	-0.402	0.219	0.067	-0.053	0.002	0.070	0.982	0.001
WASI Performance IQ	-0.007	0.054	0.902	-0.004	0.132	0.074	0.077	0.062	-0.008	0.054	0.877	-0.005	0.332	0.252	0.188	0.041	0.111	0.079	0.158	0.048
WASI Full Scale IQ	0.026	0.048	0.585	0.015	0.062	0.068	0.361	0.030	0.028	0.048	0.567	0.016	-0.074	0.225	0.741	-0.010	0.077	0.072	0.283	0.035

Key: Mercury effect = Better Outcome — < .05: p-value+; >.05, <.10: p-value

Mercury effect =Worse Outcome — < .05: p-value*; >.05, <.10: p-value

P-values shown are rounded to 3 decimal places. Therefore, a value shown as 0.050 may satisfy p<0.05 criterion if the original value was rounded up, or may not satisfy the criterion if the value was rounded down.

9.2.2.4.3. Main Effect Models with Alternative Prenatal Mercury Amount Assignments

The measure of prenatal exposure to ethylmercury was calculated as the sum of ethylmercury amounts from maternal receipt of vaccines and immune globulins received during pregnancy with the focus child. As explained in Section 7.2, different immune globulin products contained different amounts of ethylmercury, and for many receipts there was uncertainty regarding the specific product that was received. The medical charts often indicated that the immune globulin product received was “rhogam”. The uncertainty arises from the fact that while Rhogam is a specific product, the name “rhogam” is also often used as a generic term, similar to the way “kleenex” if often used as a generic term to refer to facial tissues, even though Kleenex is a specific product name. For assigning mercury content amounts to each receipt, if the chart indicated receipt of “rhogam”, we assigned a mercury amount equal to 12.75 micrograms. However, if the term “rhogam” was being used generically, then some other product may have been administered which may have contained up to 50 micrograms per dose.

Out of 88 prenatal rhogam receipts in the database, only four had a lot number or manufacturer written on the record that clearly confirmed that the receipt was the product “Rhogam”. In order to assess the sensitivity of the model results to our assumption that the remaining 84 rhogam receipts were, in fact, receipts of the product “Rhogam” and hence resulted in 12.75 micrograms of ethylmercury exposure, we created an alternative version of the prenatal exposure variable where we made an alternative assumption that each of these 84 receipts contained 50 micrograms of ethylmercury. Under the alternative assumptions, these “rhogam” receipts were higher exposure events than prenatal receipts of vaccines (influenza, tetatnus, diphtheria-tetanus, hepatitis-b). Under the original assumptions, the prenatal vaccine receipts where higher exposure events, relative to the “rhogam” receipts.

Exhibit 9.2.2.3 shows a summary of model results when the alternatively coded prenatal exposure variable (*PreNatThimer_Alt*) was substituted for the original prenatal exposure variable (*PreNatThimer*). Comparison of Exhibits 9.2.2.3 to 9.2.2.1 shows that alternative coding does not produce dramatic differences from original results. The alternative coding results in a slightly larger estimated beneficial effect of prenatal exposure on the NEPSY Speeded Naming outcome, and a slightly smaller estimate of a harmful effect on WISC III Digit Span, Backward Recall.

Exhibit 9.2.2.3 Main Effect Models (1) and (2) with Alternative Coding of Prenatal Exposure Variable (n=1,047)

	Main Effects Model (1)								Main Effects Model (2)											
	PreNatThimer_Alt				Exp07mos				PreNatThimer_Alt				HepB				Exp17mos			
Test	Est	S.E.	P	StCf	Est	S.E.	P	StCf	Est	S.E.	P	StCf	Est	S.E.	P	StCf	Est	S.E.	P	StCf
Speech and Language																				
Boston Naming Test	0.013	0.011	0.242	0.026	0.052	0.030	0.086	0.046	0.013	0.011	0.232	0.027	-0.039	0.101	0.698	-0.009	0.062	0.032	0.053	0.052
NEPSY: Speeded Naming	0.033	0.013	0.014+	0.068	0.014	0.038	0.719	0.012	0.033	0.013	0.014+	0.068	-0.051	0.126	0.683	-0.012	0.021	0.041	0.599	0.018
NEPSY: Comprehension of Instructions	0.001	0.005	0.791	0.008	-0.014	0.014	0.307	-0.035	0.001	0.005	0.783	0.008	-0.031	0.045	0.494	-0.021	-0.012	0.015	0.411	-0.028
CELF: Formulated Sentences	0.008	0.010	0.444	0.020	-0.034	0.030	0.251	-0.036	0.008	0.010	0.439	0.020	-0.074	0.099	0.455	-0.021	-0.030	0.032	0.350	-0.030
CELF: Recalling Sentences	0.018	0.022	0.415	0.021	0.002	0.062	0.980	0.001	0.018	0.022	0.410	0.021	-0.069	0.206	0.739	-0.009	0.010	0.066	0.883	0.005
GFTA: Articulation (lower = better)	-0.003	0.003	0.316	-0.030	0.011	0.010	0.253	0.041	-0.004	0.003	0.290	-0.032	0.076	0.031	0.016*	0.077	0.003	0.010	0.730	0.012
Stuttering: Assessor Rating (lower = better)	-0.004	0.012	0.752	0.879	0.026	0.033	0.435	1.441	-0.004	0.012	0.748	0.877	0.054	0.102	0.599	1.228	0.022	0.035	0.524	1.344
Stuttering: Parent Rating (lower = better)	-0.002	0.015	0.876	0.926	0.020	0.043	0.639	1.333	-0.002	0.015	0.878	0.927	-0.118	0.125	0.345	0.636	0.034	0.045	0.449	1.575
Stuttering: Teacher Rating (lower = better)	-0.011	0.010	0.307	0.701	0.009	0.025	0.731	1.131	-0.010	0.010	0.311	0.703	0.027	0.074	0.717	1.109	0.006	0.026	0.808	1.090
Verbal Memory																				
CVLT-C: Free Recall, No Delay	0.021	0.016	0.202	0.036	0.000	0.046	0.999	0.000	0.021	0.016	0.203	0.036	0.015	0.153	0.922	0.003	-0.002	0.049	0.973	-0.001
CVLT-C: Free Recall, Short Delay	0.003	0.005	0.510	0.019	-0.024	0.013	0.065	-0.063	0.003	0.005	0.512	0.019	-0.020	0.043	0.652	-0.014	-0.024	0.014	0.077	-0.060
CVLT-C: Cued Recall, Short Delay	0.000	0.004	0.924	-0.003	-0.005	0.011	0.636	-0.016	0.000	0.004	0.912	-0.003	0.026	0.038	0.499	0.020	-0.009	0.012	0.461	-0.025
CVLT-C: Free Recall, Long Delay	0.003	0.004	0.508	0.019	-0.019	0.012	0.110	-0.054	0.003	0.004	0.507	0.019	-0.024	0.040	0.556	-0.018	-0.019	0.013	0.141	-0.049
CVLT-C: Cued Recall, Long Delay	0.003	0.004	0.547	0.017	0.001	0.012	0.910	0.004	0.002	0.004	0.551	0.017	0.008	0.039	0.833	0.006	0.001	0.013	0.967	0.001
CMS Stories 1: Immediate Recall	0.022	0.021	0.292	0.024	-0.029	0.059	0.625	-0.013	0.022	0.021	0.289	0.024	-0.083	0.197	0.674	-0.010	-0.023	0.063	0.717	-0.010
CMS Stories 2: Delayed Recall	0.004	0.020	0.827	0.005	0.004	0.059	0.942	0.002	0.005	0.020	0.820	0.005	-0.069	0.193	0.720	-0.009	0.013	0.063	0.836	0.006
Achievement																				
WJIII: Letter- Word Identification	-0.006	0.013	0.669	-0.010	0.062	0.037	0.092	0.047	-0.005	0.013	0.691	-0.009	-0.085	0.122	0.488	-0.017	0.079	0.039	0.044+	0.056
Fine Motor Coordination																				
Grooved Pegboard: Dominant Hand (lower = better)	-0.048	0.032	0.130	-0.030	-0.085	0.089	0.338	-0.022	-0.048	0.032	0.135	-0.029	-0.296	0.299	0.323	-0.021	-0.062	0.094	0.511	-0.015
Grooved Pegboard: Non-dom Hand (lower = better)	-0.039	0.038	0.313	-0.021	-0.278	0.109	0.011+	-0.063	-0.039	0.038	0.312	-0.021	-0.237	0.362	0.513	-0.014	-0.283	0.116	0.015+	-0.060
Finger Tapping: Dominant Hand	-0.014	0.011	0.207	-0.034	0.033	0.031	0.282	0.035	-0.014	0.011	0.191	-0.035	0.221	0.103	0.032+	0.062	0.012	0.033	0.727	0.011
Finger Tapping: Non-dominant Hand	-0.015	0.010	0.119	-0.042	0.017	0.028	0.543	0.020	-0.015	0.010	0.118	-0.042	0.038	0.093	0.681	0.012	0.015	0.030	0.625	0.016
Visual Spatial Ability																				
Stanford Binet: Copying	0.004	0.005	0.436	0.023	0.007	0.015	0.653	0.016	0.004	0.005	0.427	0.024	-0.022	0.050	0.667	-0.014	0.010	0.016	0.530	0.023
Attention/Executive Functioning																				
GDS Vigilance Task: Correct Responses	-0.005	0.009	0.560	-0.017	0.032	0.026	0.220	0.044	-0.005	0.009	0.570	-0.017	-0.011	0.085	0.896	-0.004	0.037	0.027	0.182	0.047
GDS Vigilance Task: Errors (lower = better)	0.006	0.023	0.801	0.007	-0.020	0.067	0.762	-0.011	0.006	0.023	0.805	0.007	0.007	0.219	0.974	0.001	-0.023	0.071	0.742	-0.012
WISC III: Digit Span, Forward Recall	0.000	0.003	0.970	0.001	-0.002	0.010	0.820	-0.008	0.000	0.003	0.959	0.002	-0.017	0.032	0.594	-0.017	0.000	0.010	0.965	-0.002
WISC III: Digit Span, Backward Recall	-0.005	0.003	0.078	-0.053	0.017	0.008	0.034+	0.076	-0.005	0.003	0.075	-0.054	0.036	0.028	0.190	0.042	0.015	0.009	0.078	0.062
WISC III: Digit Span, Combined	-0.005	0.005	0.367	-0.026	0.017	0.015	0.257	0.040	-0.005	0.005	0.369	-0.026	0.012	0.048	0.798	0.008	0.017	0.015	0.273	0.038
BRIEF Parent Rating: Metacognition (lower = better)	-0.016	0.032	0.613	-0.015	-0.051	0.092	0.581	-0.020	-0.017	0.032	0.610	-0.015	0.017	0.306	0.956	0.002	-0.058	0.098	0.550	-0.021
BRIEF Teacher Rating: Metacognition (lower = better)	-0.004	0.045	0.927	-0.003	-0.145	0.132	0.274	-0.046	-0.005	0.045	0.917	-0.003	0.022	0.430	0.960	0.002	-0.164	0.140	0.243	-0.048
Behavior Regulation (lower = better)																				
CRS-R: Parent Rating: Hyperactive/Impulsive	-0.004	0.009	0.625	-0.015	0.019	0.026	0.462	0.027	-0.005	0.009	0.612	-0.015	0.074	0.087	0.397	0.028	0.013	0.028	0.640	0.017
CRS-R: Teacher Rating: Hyperactive/Impulsive	0.004	0.011	0.745	0.011	-0.046	0.034	0.170	-0.057	0.004	0.011	0.751	0.011	-0.009	0.110	0.933	-0.003	-0.050	0.036	0.157	-0.058
CRS-R: Parent Rating: Inattentive	-0.001	0.011	0.911	-0.003	-0.023	0.030	0.443	-0.028	-0.001	0.011	0.903	-0.004	0.022	0.100	0.828	0.007	-0.028	0.032	0.379	-0.031
CRS-R: Teacher Rating: Inattentive	-0.001	0.015	0.971	-0.001	-0.034	0.043	0.434	-0.033	-0.001	0.015	0.964	-0.002	0.015	0.140	0.915	0.004	-0.039	0.046	0.391	-0.036
BRIEF Parent Rating: Behavior Regulation	-0.020	0.020	0.317	-0.030	0.075	0.055	0.173	0.049	-0.019	0.020	0.326	-0.030	-0.069	0.185	0.708	-0.012	0.092	0.059	0.119	0.056
BRIEF Teacher Rating: Behavior Regulation	0.006	0.024	0.805	0.008	-0.042	0.072	0.556	-0.025	0.005	0.024	0.825	0.007	0.193	0.231	0.405	0.030	-0.070	0.076	0.360	-0.039
Tics (lower = better)																				
Motor tics (current): Assessor Rating	0.010	0.006	0.086	1.400	0.034	0.022	0.125	1.619	0.010	0.006	0.081	1.409	-0.021	0.068	0.754	0.922	0.040	0.023	0.085	1.703
Phonics tics (current): Assessor Rating	0.002	0.007	0.777	1.070	0.037	0.023	0.102	1.702	0.002	0.007	0.778	1.070	0.039	0.073	0.587	1.163	0.037	0.024	0.119	1.637
Motor tics (current): Parent Rating	0.000	0.007	0.944	0.984	-0.001	0.021	0.972	0.990	0.000	0.007	0.983	0.995	-0.106	0.069	0.126	0.668	0.012	0.022	0.591	1.171
Phonics tics (current): Parent Rating	-0.004	0.007	0.558	0.870	0.006	0.019	0.728	1.097	-0.004	0.007	0.548	0.867	0.026	0.064	0.686	1.104	0.004	0.020	0.827	1.060
General Intellectual Functioning																				
WASI Verbal IQ	0.019	0.023	0.414	0.022	-0.041	0.066	0.534	-0.020	0.020	0.023	0.392	0.023	-0.398	0.219	0.069	-0.052	-0.001	0.070	0.988	-0.001
WASI Performance IQ	0.016	0.026	0.539	0.018	0.130	0.074	0.081	0.061	0.016	0.026	0.551	0.017	0.317	0.251	0.207	0.040	0.110	0.079	0.162	0.048
WASI Full Scale IQ	0.018	0.024	0.447	0.021	0.060	0.068	0.372	0.030	0.018	0.024	0.436	0.021	-0.083	0.224	0.713	-0.011	0.077	0.072	0.286	0.035

		< .05	>.05, <.10		< .05	>.05, <.10
Key: Mercury effect = Better Outcome		p-value+	p-value	Mercury effect =Worse Outcome	p-value*	p-value

P-values shown are rounded to 3 decimal places. Therefore, a value shown as 0.050 may satisify p<0.05 criterion if the original value was rounded up, or may not satisify the criterion if the value was rounded down.

9.2.2.4.4. Additional Main Effect Models for ADHD Outcomes

Measures of attention deficit hyperactivity disorder (ADHD) symptomatology were obtained from administration of Conners and BRIEF assessments[14] to parents of teachers of focus children. There was concern among the study's external advisors that children that were on ADHD medications in the time frame that parents and teachers completed the Conners and BRIEF assessments might have lower scores than they would have had if they had not been taking the medications. In order to address the concern, the study's external advisors recommended several additional analyses, described below.

The parent interview data indicate that 38 children took ADHD medications, including two that had taken an ADHD stimulant within twelve hours of the clinical assessment. We did three sets of follow-up analyses to better understand the results for these 38 children and to assess whether the findings from the full sample (including those 38) were sensitive to the inclusion/exclusion of these 38 children from the analyses.

In the first set of analyses, we asked, how do the Conners and BRIEF scores of 38 children who took ADHD medications compare to the scores of children who did not take medications? Those analyses indicate that the children who took ADHD medications had significantly higher symptomotolgy scores on all 8 of the Conners and BRIEF assessment scales.

In the second set of analyses, we re-fit the main effects models for the 8 Conners and BRIEF outcomes, where the data from the 38 children who had taken ADHD medications were excluded.

In the third set of analyses we made binary outcome measures for each of the 8 assessments. These binary measures took the value 1 if the child was above a clinically relevant cut point[15] on the assessment scale or if the child had taken ADHD medications; and took the value zero of neither of those conditions occurred. We fit logistic regression models to tests the main effects hypotheses to these binary outcome data.

The results of the second and third analyses described above, as well as the results from the analyses on the full data set (these are the same results that are shown in Exhibit 9.2.2.1) are summarized in the Exhibit 9.2.2.4. Similar to the results from the full data set, there were no significant effects from the models where the 38 children who took ADHD medications were omitted. There were also no significant effects found in the logistic models for the binary outcomes.

[14] Conners' Rating Scales – Revised, and Brief Behavior Rating Inventory of Executive Function. See Section 7.1 for details.

[15] Children scoring above this cut-point were at the 90th percentile or above on the symptoms rated in the scale.

Exhibit 9.2.2.4 Additional Main Effect Models for ADHD Outcomes (n=1,047)

	Main Effects Model (1)								Main Effects Model (2)											
	PreNatThimer				Exp07mos				PreNatThimer				HepB				Exp17mos			
Test	Est	S.E.	P	StCf	Est	S.E.	P	StCf	Est	S.E.	P	StCf	Est	S.E.	P	StCf	Est	S.E.	P	StCf
Linear Model (These are the same results as shown in main summary table.)																				
Attention/Executive Functioning (lower = better)																				
BRIEF Parent Rating: Metacognition	0.021	0.066	0.744	0.010	-0.052	0.092	0.573	-0.020	0.021	0.066	0.750	0.010	0.009	0.307	0.976	0.001	-0.059	0.098	0.549	-0.022
BRIEF Teacher Rating: Metacognition	0.026	0.088	0.764	0.010	-0.147	0.133	0.268	-0.046	0.024	0.088	0.784	0.009	0.011	0.431	0.980	0.001	-0.165	0.140	0.241	-0.049
Behavior Regulation (lower = better)																				
CRS-R: Parent Rating: Hyperactive/Impulsive	0.007	0.019	0.725	0.011	0.019	0.026	0.469	0.026	0.006	0.019	0.745	0.010	0.071	0.087	0.414	0.027	0.013	0.028	0.641	0.017
CRS-R: Teacher Rating: Hyperactive/Impulsive	0.023	0.022	0.301	0.033	-0.048	0.034	0.157	-0.059	0.023	0.022	0.310	0.032	-0.016	0.110	0.883	-0.005	-0.051	0.036	0.150	-0.059
CRS-R: Parent Rating: Inattentive	0.011	0.022	0.606	0.016	-0.024	0.030	0.433	-0.028	0.011	0.022	0.619	0.015	0.019	0.100	0.848	0.006	-0.028	0.032	0.374	-0.032
CRS-R: Teacher Rating: Inattentive	0.002	0.029	0.939	0.002	-0.034	0.043	0.432	-0.033	0.002	0.029	0.957	0.002	0.014	0.141	0.919	0.004	-0.039	0.046	0.390	-0.036
BRIEF Parent Rating: Behavior Regulation	-0.021	0.040	0.594	-0.016	0.077	0.055	0.167	0.050	-0.020	0.040	0.616	-0.015	-0.069	0.185	0.711	-0.012	0.093	0.059	0.115	0.057
BRIEF Teacher Rating: Behavior Regulation	0.035	0.048	0.455	0.024	-0.045	0.072	0.535	-0.026	0.032	0.048	0.498	0.022	0.182	0.231	0.432	0.029	-0.071	0.076	0.353	-0.039
Linear Model (excluding n=39 children whose mothers indicated that child takes drugs for ADHD)																				
Attention/Executive Functioning (lower = better)																				
BRIEF Parent Rating: Metacognition	-0.008	0.066	0.902	-0.004	-0.033	0.091	0.719	-0.013	-0.009	0.066	0.892	-0.004	0.051	0.304	0.867	0.005	-0.042	0.097	0.663	-0.016
BRIEF Teacher Rating: Metacognition	-0.008	0.090	0.927	-0.003	-0.147	0.133	0.270	-0.046	-0.012	0.090	0.890	-0.005	0.117	0.433	0.787	0.010	-0.177	0.141	0.210	-0.052
Behavior Regulation (lower = better)																				
CRS-R: Parent Rating: Hyperactive/Impulsive	-0.003	0.018	0.882	-0.004	0.020	0.025	0.426	0.028	-0.003	0.018	0.855	-0.005	0.082	0.085	0.338	0.031	0.013	0.027	0.624	0.017
CRS-R: Teacher Rating: Hyperactive/Impulsive	0.012	0.022	0.582	0.018	-0.059	0.034	0.081	-0.072	0.011	0.022	0.616	0.016	0.019	0.109	0.862	0.006	-0.067	0.035	0.059	-0.077
CRS-R: Parent Rating: Inattentive	0.001	0.021	0.957	0.002	-0.011	0.029	0.719	-0.013	0.001	0.021	0.967	0.001	0.018	0.098	0.855	0.006	-0.014	0.031	0.659	-0.015
CRS-R: Teacher Rating: Inattentive	-0.010	0.029	0.722	-0.012	-0.032	0.043	0.466	-0.031	-0.011	0.029	0.693	-0.013	0.052	0.140	0.710	0.014	-0.041	0.046	0.373	-0.037
BRIEF Parent Rating: Behavior Regulation	-0.038	0.040	0.336	-0.029	0.083	0.055	0.133	0.054	-0.037	0.040	0.351	-0.029	-0.045	0.184	0.805	-0.008	0.097	0.058	0.097	0.059
BRIEF Teacher Rating: Behavior Regulation	0.000	0.048	0.996	0.000	-0.050	0.071	0.484	-0.029	-0.005	0.048	0.924	-0.003	0.230	0.229	0.316	0.036	-0.082	0.075	0.275	-0.045
Logistic Model (Outcome = 1 if child takes drugs for ADHD or if child scored above criterion on Conners/Brief assessments)																				
Attention/Executive Functioning (lower = better)																				
BRIEF Parent Rating: Metacognition	-0.002	0.011	0.872		-0.005	0.016	0.745		-0.002	0.011	0.861		0.027	0.053	0.613		-0.009	0.017	0.605	
BRIEF Teacher Rating: Metacognition	-0.005	0.010	0.634		-0.003	0.016	0.844		-0.005	0.010	0.636		-0.007	0.049	0.888		-0.003	0.017	0.875	
Behavior Regulation (lower = better)																				
CRS-R: Parent Rating: Hyperactive/Impulsive	-0.010	0.013	0.405		0.006	0.015	0.693		-0.011	0.013	0.402		0.016	0.050	0.756		0.005	0.016	0.759	
CRS-R: Teacher Rating: Hyperactive/Impulsive	0.010	0.011	0.366		-0.005	0.020	0.790		0.010	0.011	0.361		-0.015	0.062	0.815		-0.004	0.021	0.840	
CRS-R: Parent Rating: Inattentive	0.006	0.011	0.582		-0.025	0.016	0.113		0.006	0.011	0.582		-0.026	0.055	0.636		-0.025	0.017	0.136	
CRS-R: Teacher Rating: Inattentive	-0.003	0.012	0.808		0.010	0.019	0.589		-0.003	0.012	0.815		-0.009	0.057	0.880		0.012	0.020	0.533	
BRIEF Parent Rating: Behavior Regulation	-0.003	0.013	0.841		0.021	0.018	0.238		-0.003	0.013	0.844		0.007	0.059	0.903		0.023	0.019	0.230	
BRIEF Teacher Rating: Behavior Regulation	0.002	0.011	0.825		0.001	0.018	0.940		0.002	0.011	0.836		0.017	0.055	0.756		-0.001	0.019	0.976	

Key: Mercury effect = Better Outcome — < .05: p-value+; >.05, <.10: p-value

Mercury effect =Worse Outcome — < .05: p-value*; >.05, <.10: p-value

P-values shown are rounded to 3 decimal places. Therefore, a value shown as 0.050 may satisify p<0.05 criterion if the original value was rounded up, or may not satisfy the criterion if the value was rounded down.

9.2.3. Sex-by-Exposure Interaction Models

9.2.3.1. Introduction

The decision to test for differential exposure effects for boys and girls was motivated by two considerations. The first was that the design of the current study was strongly influenced by precedents set in the Faroe and Seychelles Island studies (Grandjean et. al, 1997; Davidson et. al 1998), and the Davidson study had tested for sex-by-exposure interaction effects. The second consideration was that among the types of neurodevelopmental outcomes measured in the current study, the frequency and severity of delays or problems in the general population are often unequal for boys and girls, thus generating the question of whether differential sensitivity to exposure might be related to differential performance on the outcome measures.

The analysis summaries shown in this section present results of tests for interactions of sex with prenatal exposure, cumulative exposure from birth to seven months, neonatal exposure, and cumulative exposure from 1 to seven months. A commonly used reporting convention is to report separate estimates of exposure effects for boys and girls only if the interaction meets a pre-specified criterion for statistical significance. In this convention, whenever the interaction is non-significant, only the combined effect for both boys and girls is reported. For this report we have chosen not to adopt that reporting convention. Instead, we report separate estimates of exposure effects, for boys and girls, regardless of the result of the interaction test. We felt that the readers of this report would be better served by having the more detailed set of results, even if the additional detail presents them with greater challenges in terms of interpretation of results.

9.2.3.2. Model Specifications

The notation and variables shown in the model specifications below are defined in Chapters 8. For tics and stuttering outcomes, logistic regression models that are analogous to the linear regression models specified below, were fit to the data.

Interaction Model (1): Sex by Prenatal, and Birth-7 Month Exposures

The model shown below was used to estimate separate exposure effects for males and females, and to test whether sex is an effect modifier for thimerosal exposure received either by the mother during pregnancy (prenatal exposure) or received by the child during period spanning birth to seven months of age. Sex is expressed as a dummy variable, which takes the value 1 if the child is male, and takes the value zero if the child is female.

$$Y = \beta_0 + \beta_1 preNatThimer + \beta_2 Exp07mos + \beta_3 Sexmale +$$
$$\beta_4 preNatThimer * Sexmale +$$
$$\beta_5 Exp07mos * Sexmale +$$
$$\sum_j \alpha_j oe_j + \sum_k \alpha_{j+k} cf_k + \sum_l \alpha_{j+k+l} St_l + \varepsilon$$

$\hat{\beta}_1$	=	The estimated effect of prenatal exposure to ethylmercury from vaccines and immune globulins received by the mother during pregnancy, for females.
$\hat{\beta}_2$	=	The estimated effect of cumulative exposure to ethylmercury from vaccines and immune globulins received by the child during the age range from birth to seven months, for females.
$\hat{\beta}_3$	=	The average difference between males and females on the outcome measure, after controlling for other terms in the model.
$\hat{\beta}_4$	=	The average difference between males and females in the effect of prenatal exposure.
$\hat{\beta}_1 + \hat{\beta}_4$	=	The estimated effect of prenatal exposure to ethylmercury from vaccines and immune globulins received by the mother, for males.
$\hat{\beta}_5$	=	The average difference between males and females in the effect of postnatal exposure.
$\hat{\beta}_2 + \hat{\beta}_5$	=	The estimated effect of exposure to ethylmercury from vaccines and immune globulins received by the child during the age range from birth to seven months, for males.
$\hat{\alpha}_j ... \hat{\alpha}_{j+k+l}$	=	Parameter estimates corresponding to model covariates. See Chapter 8 for details.

The model resulted in two tests of the null hypotheses that exposure effects are equal to zero for females:

$$H_0 : \beta_1 = 0 \quad vs \quad H_a : \beta_1 \neq 0$$
$$H_0 : \beta_2 = 0 \quad vs \quad H_a : \beta_2 \neq 0$$

The model also resulted in two tests of the null hypotheses that exposure effects are equal to zero for males:

$$H_0 : \beta_1 + \beta_4 = 0 \quad vs \quad H_a : \beta_1 + \beta_4 \neq 0$$
$$H_0 : \beta_2 + \beta_5 = 0 \quad vs \quad H_a : \beta_2 + \beta_5 \neq 0$$

And, the model resulted in two tests of the null hypotheses that the interaction coefficients are equal to zero.

$$H_0 : \beta_4 = 0 \quad vs \quad H_a : \beta_4 \neq 0$$
$$H_0 : \beta_5 = 0 \quad vs \quad H_a : \beta_5 \neq 0$$

All tests were conducted using the $p<0.05$ criterion[16].

Interaction Model (2): Sex by Prenatal, HepB at Birth, and 1-7 Month Exposures

The model shown below is similar to the previous model except that postnatal exposures are separated into two time periods – birth to 28 days (represented by the *HepB* variable),

[16] Since there is generally less power to detect interaction effects than main effects, it is not uncommon to specify higher alpha levels for interaction tests. However, for the sake of consistency and simplicity, we have elected to use a single alpha level criterion ($p<0.05$) for all tests of exposure effects.

and cumulative exposures during the periods spanning 29 days to 7 months of age (represented by the *Exp17mos* variable). As before, the model was used to estimate separate exposure effects for males and females, and to test whether sex is an effect modifier for prenatal or postnatal exposures.

$$Y = \beta_0 + \beta_1 preNatThimer + \beta_2 HepB + \beta_3 Exp17mos +$$
$$+ \beta_4 sexmale$$
$$+ \beta_5 preNatThimer * sexmale + \beta_6 HepB * sexmale + \beta_7 Exp17mos * sexmale +$$
$$\sum_j \alpha_j oe_j + \sum_k \alpha_{j+k} cf_k + \sum_l \alpha_{j+k+l} St_l + \varepsilon$$

$\hat{\beta}_1$	=	The estimated effect of prenatal exposure to ethylmercury from vaccines and immune globulins received by the mother, for females.
$\hat{\beta}_2$	=	The estimated effect of exposure to ethylmercury from vaccines and immune globulins received by the child during the age range from birth to one month (28 days), for females.
$\hat{\beta}_3$	=	The estimated effect of exposure to ethylmercury from vaccines received by the child during the age range from one month (29 days) to seven months, for females.
$\hat{\beta}_4$	=	The average difference between males and females on the outcome measure, after controlling for other terms in the model.
$\hat{\beta}_5$	=	The average difference between males and females in the effect of prenatal exposure.
$\hat{\beta}_1 + \hat{\beta}_5$	=	The estimated effect of prenatal exposure to ethylmercury from vaccines and immune globulins received by the mother, for males.
$\hat{\beta}_6$	=	The average difference between males and females in the effects of exposures received during the age range spanning birth to 1 month (28 days).
$\hat{\beta}_2 + \hat{\beta}_6$	=	The estimated effect of exposure to ethylmercury from vaccines and immune globulins received by the child during the age range from birth to one month, for males.
$\hat{\beta}_7$	=	The average difference between males and females in the effects of exposures received during the age range spanning one to seven months.
$\hat{\beta}_3 + \hat{\beta}_7$	=	The estimated effect of exposure to ethylmercury from vaccines and immune globulins received by the child during the age range from one to seven months, for males.
$\hat{\alpha}_j ... \hat{\alpha}_{j+k+l}$	=	Parameter estimates corresponding to model covariates. See Chapter 8 for details.

The model resulted in three tests of the null hypotheses that exposure effects are equal to zero for females:

$$H_0 : \beta_1 = 0 \quad vs \quad H_a : \beta_1 \neq 0$$
$$H_0 : \beta_2 = 0 \quad vs \quad H_a : \beta_2 \neq 0$$
$$H_0 : \beta_3 = 0 \quad vs \quad H_a : \beta_3 \neq 0$$

The model also resulted in three tests of the null hypotheses that exposure effects are equal to zero for males:

$$H_0 : \beta_1 + \beta_5 = 0 \quad vs \quad H_a : \beta_1 + \beta_5 \neq 0$$
$$H_0 : \beta_2 + \beta_6 = 0 \quad vs \quad H_a : \beta_2 + \beta_6 \neq 0$$
$$H_0 : \beta_3 + \beta_7 = 0 \quad vs \quad H_a : \beta_3 + \beta_7 \neq 0$$

And, the model resulted in three tests of the null hypotheses that the interaction coefficients are equal to zero.

$$H_0 : \beta_5 = 0 \quad vs \quad H_a : \beta_5 \neq 0$$
$$H_0 : \beta_6 = 0 \quad vs \quad H_a : \beta_6 \neq 0$$
$$H_0 : \beta_7 = 0 \quad vs \quad H_a : \beta_7 \neq 0$$

9.2.3.3. Results

The results summarized in Exhibits 9.2.3.1 and 9.2.3.2 correspond to models fit to the full data set and show the estimated exposure effects on females and males, respectively. For each of the two sexes, there is an approximate balance between the number of significant effects that are in the direction of harm and benefit.

9.2.3.3.1. Prenatal Exposure

There are four significant sex-by-prenatal-exposure interaction effects shown in the summary tables. They are indicated by and "S*" next to the parameter estimate. For the *Stanford Binet Copying* outcome measure, the interaction effect was such that the estimated exposure effect for males was significant and beneficial, whereas the estimated exposure effect was non-significant and in the direction of harm for females. For the remaining three outcome measures with significant sex-by-prenatal-exposure interactions, the estimated effects were in the direction of harm for one sex, but in the direction of benefit for the other. In none of these was the estimated exposure effect significantly different than zero for either sex.

For males, the estimated effect of prenatal exposure on performance of the *WISC III Digit Span Backwards Recall* tests was significant and in the direction of harm. Although the interaction test was not significant, indicating that we cannot reject the null hypothesis of a common effect for males and females, the estimate for females was non-significant, but also in the direction of harm.

9.2.3.3.2. Cumulative Exposure Birth to Seven Months

There is one significant sex-by-birth-to-seven-months-exposure interaction effect shown in the summary tables. It corresponds to the *Parent Rated Phonic Tics* outcome measure, and it is such that estimated effect is in the direction of harm for males, but is similar in

magnitude but in the direction of benefit for females, and is non-significant for both sexes.

There were three outcome measures where the estimated effects of cumulative exposure in the age range spanning birth to seven months was associated with significant harmful effects for males. However, there were also three outcome measures where the estimated exposure effects were significant and beneficial. One was for males and two were for females.

The estimated effects of exposures in the age range of one to seven months are very similar to the estimated birth to seven month exposure effects, and are not discussed further.

9.2.3.3.3. Neonatal Exposure (Birth to 28 Days)

There are six significant sex-by-neonatal-exposure interaction effects shown in the summary tables. All are such that the estimated effects are in the direction of harm for one sex, but in the direction of benefit for the other. In only one was the estimated exposure effect significantly different than zero for either sex. That is the estimated beneficial effect of increased exposure on the *Finger Tapping Non-dominant Hand* outcome measure for males.

For females, increased neonatal exposure was associated with poorer scores on the *WASI Verbal IQ* measure, whereas increased neonatal exposure was associated with better scores on the *WASI Performance IQ* measure for males. Increased neonatal exposure was associated with beneficial effects on *Parent Rated Motor Tics* for females, and for *Finger Tapping Dominant and Non-dominant Hands* for males.

Exhibit 9.2.3.1. Summary of Thimerosal Effects for Females (n=1,047; Data set included 538 females and 509 males)

	Model (1)								Model (2)											
	PreNatThimer				Exp07mos				PreNatThimer				HepB				Exp17mos			
Test	Est	S.E.	P	StCf	Est	S.E.	P	StCf	Est	S.E.	P	StCf	Est	S.E.	P	StCf	Est	S.E.	P	StCf
Speech and Language																				
Boston Naming Test	0.027	0.035	0.441	0.028	0.060	0.040	0.131	0.054	0.031	0.035	0.385	0.032	-0.147	0.141	0.300	-0.035	0.080	0.042	0.056	0.067
NEPSY: Speeded Naming	0.046	0.044	0.297	0.047	0.027	0.050	0.588	0.024	0.047	0.044	0.288	0.048	-0.026	0.177	0.882	-0.006	0.033	0.053	0.530	0.027
NEPSY: Comprehension of Instructions	0.003	0.016	0.831	0.010	-0.007	0.018	0.676	-0.019	0.005	0.016	0.746	0.015	S -0.113	0.063	0.075	-0.076	0.003	0.019	0.875	0.007
CELF: Formulated Sentences	0.026	0.035	0.456	0.032	-0.044	0.039	0.262	-0.047	0.027	0.035	0.429	0.034	-0.146	0.139	0.295	-0.041	-0.034	0.041	0.409	-0.034
CELF: Recalling Sentences	0.058	0.072	0.418	0.034	0.011	0.081	0.888	0.006	0.061	0.072	0.396	0.036	-0.157	0.289	0.585	-0.021	0.028	0.086	0.745	0.013
GFTA: Articulation (lower = better)	-0.005	0.011	0.683	-0.020	0.008	0.013	0.533	0.030	-0.006	0.011	0.601	-0.026	0.073	0.044	0.098	0.075	0.001	0.013	0.937	0.004
Stuttering: Assessor Rating (lower = better)	0.037	0.024	0.120	1.847	0.025	0.045	0.571	1.439	0.037	0.024	0.119	1.855	-0.001	0.155	0.997	0.998	0.028	0.047	0.556	1.449
Stuttering: Parent Rating (lower = better)	-0.717	8.949	0.936	0.000	0.038	0.062	0.536	1.726	-0.715	8.701	0.935	0.000	-0.141	0.195	0.468	0.583	0.051	0.064	0.419	1.982
Stuttering: Teacher Rating (lower = better)	-0.046	0.049	0.348	0.467	0.005	0.038	0.901	1.071	-0.046	0.049	0.352	0.467	-0.095	0.123	0.441	0.695	0.011	0.039	0.772	1.163
Verbal Memory																				
CVLT-C: Free Recall, No Delay	0.033	0.054	0.543	0.028	-0.006	0.060	0.918	-0.005	0.036	0.054	0.502	0.031	-0.203	0.215	0.345	-0.040	0.012	0.064	0.853	0.008
CVLT-C: Free Recall, Short Delay	-0.001	0.015	0.922	-0.005	-0.028	0.017	0.106	-0.072	-0.001	0.015	0.959	-0.002	-0.072	0.061	0.243	-0.050	-0.023	0.018	0.195	-0.057
CVLT-C: Cued Recall, Short Delay	-0.007	0.013	0.577	-0.026	-0.009	0.015	0.529	-0.028	-0.007	0.013	0.599	-0.024	S -0.044	0.053	0.412	-0.035	-0.006	0.016	0.691	-0.017
CVLT-C: Free Recall, Long Delay	-0.008	0.014	0.566	-0.026	-0.016	0.016	0.314	-0.045	-0.007	0.014	0.615	-0.023	-0.072	0.057	0.204	-0.054	-0.011	0.017	0.522	-0.028
CVLT-C: Cued Recall, Long Delay	-0.008	0.014	0.541	-0.028	-0.002	0.016	0.898	-0.006	-0.007	0.014	0.600	-0.024	S* -0.069	0.055	0.212	-0.053	0.004	0.016	0.813	0.011
CMS Stories 1: Immediate Recall	-0.021	0.069	0.765	-0.011	0.025	0.078	0.751	0.011	-0.018	0.069	0.792	-0.010	-0.110	0.276	0.690	-0.014	0.037	0.082	0.648	0.016
CMS Stories 2: Delayed Recall	-0.060	0.068	0.372	-0.033	0.039	0.077	0.616	0.018	-0.056	0.068	0.410	-0.031	-0.199	0.272	0.463	-0.025	0.061	0.081	0.453	0.027
Achievement																				
WJIII: Letter- Word Identification	-0.025	0.043	0.557	-0.022	S 0.009	0.048	0.856	0.007	-0.021	0.043	0.620	-0.019	-0.205	0.171	0.232	-0.042	0.030	0.051	0.552	0.022
Fine Motor Coordination																				
Grooved Pegboard: Dominant Hand (lower = better)	-0.046	0.105	0.658	-0.014	-0.054	0.117	0.645	-0.014	-0.044	0.105	0.678	-0.013	-0.155	0.419	0.712	-0.011	-0.042	0.123	0.732	-0.010
Grooved Pegboard: Non-dom Hand (lower = better)	-0.035	0.126	0.783	-0.009	-0.344	0.143	0.016 +	-0.078	-0.035	0.127	0.781	-0.009	-0.316	0.509	0.535	-0.019	-0.347	0.151	0.022 +	-0.073
Finger Tapping: Dominant Hand	0.001	0.036	0.969	0.002	0.007	0.041	0.856	0.008	0.000	0.036	0.994	0.000	S 0.026	0.144	0.859	0.007	0.003	0.043	0.950	0.003
Finger Tapping: Non-dominant Hand	0.024	0.033	0.470	0.031	-0.006	0.037	0.871	-0.007	0.027	0.033	0.412	0.036	S* -0.204	0.131	0.118	-0.062	0.013	0.039	0.745	0.014
Visual Spatial Ability																				
Stanford Binet: Copying	S* -0.033	0.017	0.057	-0.093	S 0.028	0.020	0.163	0.066	S* -0.032	0.018	0.065	-0.090	-0.029	0.071	0.685	-0.018	S 0.033	0.021	0.113	0.074
Attention/Executive Functioning																				
GDS Vigilance Task: Correct Responses	-0.014	0.030	0.647	-0.022	0.036	0.034	0.282	0.050	-0.011	0.030	0.710	-0.018	-0.105	0.119	0.378	-0.039	0.050	0.036	0.159	0.065
GDS Vigilance Task: Errors (lower = better)	0.040	0.077	0.600	0.025	-0.111	0.087	0.201	-0.060	0.038	0.077	0.617	0.024	-0.007	0.308	0.981	-0.001	-0.121	0.092	0.189	-0.061
WISC III: Digit Span, Forward Recall	S* -0.017	0.011	0.119	-0.076	-0.003	0.012	0.787	-0.013	S* -0.017	0.011	0.118	-0.076	0.004	0.044	0.928	0.004	-0.004	0.013	0.775	-0.013
WISC III: Digit Span, Backward Recall	-0.004	0.010	0.656	-0.022	0.025	0.011	0.021 +	0.109	-0.004	0.010	0.654	-0.022	0.020	0.039	0.610	0.023	0.025	0.011	0.027 +	0.102
WISC III: Digit Span, Combined	-0.021	0.017	0.208	-0.060	0.022	0.019	0.258	0.052	-0.021	0.017	0.211	-0.060	0.018	0.068	0.788	0.012	0.022	0.020	0.276	0.050
BRIEF Parent Rating: Metacognition (lower = better)	S* -0.159	0.107	0.138	-0.073	-0.082	0.120	0.494	-0.032	S* -0.155	0.107	0.150	-0.071	-0.345	0.431	0.423	-0.036	-0.058	0.127	0.649	-0.021
BRIEF Teacher Rating: Metacognition (lower = better)	-0.042	0.143	0.769	-0.016	-0.177	0.174	0.308	-0.056	-0.031	0.144	0.829	-0.011	S* -0.826	0.596	0.166	-0.070	-0.126	0.182	0.489	-0.037
Behavior Regulation (lower = better)																				
CRS-R: Parent Rating: Hyperactive/Impulsive	-0.019	0.030	0.529	-0.031	-0.001	0.034	0.972	-0.002	-0.019	0.030	0.529	-0.031	-0.011	0.122	0.929	-0.004	-0.001	0.036	0.978	-0.001
CRS-R: Teacher Rating: Hyperactive/Impulsive	0.011	0.037	0.755	0.016	-0.055	0.045	0.219	-0.068	0.013	0.037	0.716	0.019	-0.186	0.153	0.225	-0.061	-0.044	0.046	0.339	-0.051
CRS-R: Parent Rating: Inattentive	S* -0.048	0.035	0.175	-0.067	-0.020	0.039	0.609	-0.024	S* -0.047	0.035	0.180	-0.066	-0.061	0.141	0.664	-0.020	-0.017	0.042	0.690	-0.019
CRS-R: Teacher Rating: Inattentive	0.001	0.047	0.986	0.001	-0.070	0.057	0.222	-0.068	0.004	0.047	0.931	0.005	S* -0.312	0.195	0.109	-0.081	-0.051	0.059	0.393	-0.046
BRIEF Parent Rating: Behavior Regulation	-0.060	0.065	0.353	-0.046	S -0.008	0.073	0.912	-0.005	-0.055	0.065	0.396	-0.042	-0.280	0.260	0.282	-0.049	0.019	0.077	0.805	0.012
BRIEF Teacher Rating: Behavior Regulation	0.013	0.077	0.871	0.009	-0.084	0.095	0.376	-0.049	0.013	0.078	0.872	0.009	-0.104	0.322	0.746	-0.016	-0.088	0.099	0.373	-0.049
Tics (lower = better)																				
Motor tics (current): Assessor Rating	0.033	0.020	0.104	1.733	0.003	0.030	0.928	1.039	0.036	0.020	0.083	1.806	S -0.174	0.108	0.109	0.515	0.020	0.031	0.531	1.300
Phonics tics (current): Assessor Rating	-0.029	0.046	0.529	0.620	S -0.002	0.033	0.945	0.969	-0.029	0.046	0.532	0.621	-0.078	0.115	0.498	0.743	0.004	0.034	0.899	1.059
Motor tics (current): Parent Rating	-0.052	0.054	0.335	0.424	-0.008	0.030	0.788	0.891	-0.051	0.054	0.344	0.425	-0.234	0.108	0.030 +	0.409	0.016	0.032	0.624	1.234
Phonics tics (current): Parent Rating	-0.069	0.051	0.182	0.320	S* -0.038	0.026	0.149	0.584	-0.070	0.052	0.173	0.310	0.030	0.101	0.768	1.121	S* -0.044	0.028	0.115	0.559
General Intellectual Functioning																				
WASI Verbal IQ	0.039	0.076	0.607	0.022	-0.097	0.086	0.263	-0.047	0.051	0.076	0.508	0.029	-0.738	0.307	0.017 *	-0.097	-0.035	0.091	0.696	-0.016
WASI Performance IQ	-0.032	0.092	0.726	-0.018	0.113	0.098	0.246	0.053	-0.029	0.092	0.756	-0.016	S* -0.211	0.349	0.546	-0.026	0.140	0.103	0.173	0.061
WASI Full Scale IQ	-0.005	0.082	0.948	-0.003	0.044	0.089	0.622	0.021	0.004	0.082	0.957	0.002	S* -0.519	0.313	0.098	-0.068	0.097	0.093	0.299	0.044

Key: Mercury effect = Better Outcome — < .05: p-value+; >.05, <.10: p-value

Mercury effect =Worse Outcome — < .05: p-value*; >.05, <.10: p-value

P-values shown are rounded to 3 decimal places. Therefore, a value shown as 0.050 may satisfy p<0.05 criterion if the original value was rounded up, or may not satisfy the criterion if the value was rounded down.
S* (S) = Coefficient for females is significantly different than coefficient for males at the 0.05 (0.10) level

Exhibit 9.2.3.2. Summary of Thimerosal Effects for Males (n=1,047; Data set included 538 females and 509 males)

	Model (1)								Model (2)											
	PreNatThimer				Exp07mos				PreNatThimer				HepB				Exp17mos			
Test	Est	S.E.	P	StCf	Est	S.E.	P	StCf	Est	S.E.	P	StCf	Est	S.E.	P	StCf	Est	S.E.	P	StCf
Speech and Language																				
Boston Naming Test	0.034	0.027	0.207	0.036	0.041	0.040	0.304	0.036	0.035	0.027	0.195	0.037	0.062	0.141	0.658	0.015	0.037	0.043	0.386	0.031
NEPSY: Speeded Naming	0.064	0.034	0.059	0.066	-0.006	0.050	0.899	-0.006	0.064	0.034	0.058	0.066	-0.085	0.177	0.631	-0.020	0.004	0.054	0.948	0.003
NEPSY: Comprehension of Instructions	-0.004	0.012	0.714	-0.013	-0.020	0.018	0.258	-0.051	-0.004	0.012	0.737	-0.012	S 0.053	0.063	0.401	0.036	-0.029	0.019	0.131	-0.069
CELF: Formulated Sentences	0.017	0.027	0.515	0.021	-0.027	0.039	0.488	-0.029	0.018	0.027	0.507	0.022	-0.012	0.137	0.930	-0.003	-0.029	0.042	0.491	-0.029
CELF: Recalling Sentences	0.059	0.056	0.294	0.034	-0.014	0.081	0.864	-0.007	0.059	0.056	0.289	0.034	0.003	0.288	0.991	0.000	-0.016	0.088	0.854	-0.008
GFTA: Articulation (lower = better)	0.000	0.009	0.990	0.000	0.014	0.012	0.259	0.053	0.000	0.009	0.970	-0.001	0.077	0.044	0.076	0.079	0.006	0.014	0.650	0.022
Stuttering: Assessor Rating (lower = better)	-0.466	1.145	0.684	0.000	0.025	0.040	0.537	1.422	-0.465	1.136	0.682	0.000	0.077	0.129	0.552	1.340	0.017	0.044	0.693	1.257
Stuttering: Parent Rating (lower = better)	-0.005	0.043	0.912	0.925	0.008	0.052	0.870	1.129	-0.005	0.044	0.918	0.928	-0.100	0.161	0.534	0.683	0.020	0.055	0.715	1.310
Stuttering: Teacher Rating (lower = better)	-0.039	0.036	0.283	0.521	0.014	0.030	0.645	1.214	-0.036	0.035	0.300	0.545	0.095	0.089	0.288	1.436	0.002	0.032	0.962	1.021
Verbal Memory																				
CVLT-C: Free Recall, No Delay	0.026	0.042	0.533	0.022	0.003	0.061	0.954	0.003	0.027	0.042	0.523	0.023	0.225	0.213	0.291	0.044	-0.025	0.066	0.709	-0.017
CVLT-C: Free Recall, Short Delay	-0.001	0.012	0.909	-0.004	-0.020	0.017	0.233	-0.053	-0.001	0.012	0.925	-0.003	0.032	0.060	0.594	0.022	-0.027	0.018	0.147	-0.065
CVLT-C: Cued Recall, Short Delay	0.003	0.010	0.784	0.010	-0.002	0.015	0.917	-0.005	0.003	0.010	0.762	0.011	S 0.094	0.052	0.072	0.075	-0.013	0.016	0.405	-0.037
CVLT-C: Free Recall, Long Delay	0.006	0.011	0.562	0.021	-0.023	0.016	0.144	-0.065	0.006	0.011	0.550	0.021	0.028	0.056	0.618	0.021	-0.029	0.017	0.085	-0.077
CVLT-C: Cued Recall, Long Delay	0.013	0.011	0.236	0.043	0.004	0.016	0.800	0.011	0.013	0.011	0.231	0.043	S* 0.087	0.055	0.115	0.067	-0.007	0.017	0.696	-0.018
CMS Stories 1: Immediate Recall	0.051	0.053	0.329	0.028	-0.086	0.078	0.267	-0.040	0.052	0.053	0.325	0.028	-0.037	0.274	0.893	-0.005	-0.093	0.084	0.272	-0.040
CMS Stories 2: Delayed Recall	0.022	0.052	0.678	0.012	-0.029	0.076	0.705	-0.014	0.022	0.052	0.670	0.012	0.086	0.270	0.749	0.011	-0.043	0.083	0.600	-0.019
Achievement																				
WJIII: Letter- Word Identification	0.030	0.033	0.358	0.027	S 0.113	0.048	0.019 +	0.086	0.031	0.033	0.347	0.027	0.022	0.170	0.897	0.004	0.124	0.052	0.018 +	0.088
Fine Motor Coordination																				
Grooved Pegboard: Dominant Hand (lower = better)	-0.145	0.081	0.073	-0.044	-0.103	0.117	0.378	-0.027	-0.145	0.081	0.073	-0.044	-0.419	0.417	0.315	-0.029	-0.065	0.127	0.609	-0.016
Grooved Pegboard: Non-dom Hand (lower = better)	-0.115	0.098	0.242	-0.030	-0.203	0.143	0.155	-0.046	-0.115	0.098	0.242	-0.030	-0.161	0.504	0.750	-0.010	-0.208	0.155	0.180	-0.044
Finger Tapping: Dominant Hand	-0.025	0.028	0.364	-0.031	0.062	0.041	0.130	0.065	-0.024	0.027	0.375	-0.030	S 0.411	0.144	0.004 +	0.115	0.018	0.044	0.681	0.018
Finger Tapping: Non-dominant Hand	-0.038	0.025	0.126	-0.051	0.043	0.037	0.244	0.049	-0.037	0.025	0.138	-0.049	S* 0.268	0.129	0.038 +	0.082	0.015	0.040	0.714	0.016
Visual Spatial Ability																				
Stanford Binet: Copying	S* 0.029	0.014	0.033 +	0.080	S -0.015	0.020	0.444	-0.036	S* 0.029	0.014	0.032 +	0.081	-0.004	0.070	0.960	-0.002	S -0.017	0.021	0.441	-0.037
Attention/Executive Functioning																				
GDS Vigilance Task: Correct Responses	-0.013	0.023	0.580	-0.021	0.028	0.034	0.398	0.039	-0.012	0.023	0.596	-0.020	0.088	0.119	0.457	0.033	0.021	0.037	0.569	0.027
GDS Vigilance Task: Errors (lower = better)	0.025	0.060	0.674	0.016	0.066	0.087	0.444	0.036	0.025	0.060	0.677	0.016	-0.013	0.305	0.966	-0.002	0.076	0.094	0.418	0.038
WISC III: Digit Span, Forward Recall	S* 0.010	0.009	0.220	0.046	-0.001	0.012	0.924	-0.004	S* 0.011	0.009	0.219	0.046	-0.036	0.044	0.419	-0.036	0.003	0.014	0.815	0.011
WISC III: Digit Span, Backward Recall	-0.018	0.007	0.015 *	-0.091	0.011	0.011	0.288	0.050	-0.018	0.007	0.016 *	-0.090	0.055	0.038	0.148	0.065	0.006	0.012	0.616	0.024
WISC III: Digit Span, Combined	-0.006	0.013	0.619	-0.018	0.012	0.019	0.512	0.030	-0.006	0.013	0.620	-0.018	0.013	0.068	0.851	0.008	0.012	0.021	0.550	0.028
BRIEF Parent Rating: Metacognition (lower = better)	S* 0.128	0.083	0.123	0.058	-0.030	0.120	0.803	-0.012	S* 0.129	0.083	0.119	0.059	0.388	0.423	0.360	0.041	-0.082	0.130	0.528	-0.030
BRIEF Teacher Rating: Metacognition (lower = better)	0.068	0.112	0.546	0.025	-0.121	0.172	0.483	-0.038	0.063	0.112	0.570	0.023	S* 0.904	0.606	0.137	0.076	-0.251	0.187	0.179	-0.074
Behavior Regulation (lower = better)																				
CRS-R: Parent Rating: Hyperactive/Impulsive	0.021	0.023	0.369	0.034	0.038	0.034	0.266	0.053	0.021	0.023	0.368	0.034	0.156	0.121	0.200	0.058	0.023	0.037	0.533	0.030
CRS-R: Teacher Rating: Hyperactive/Impulsive	0.029	0.028	0.291	0.042	-0.042	0.044	0.341	-0.052	0.029	0.028	0.294	0.042	0.159	0.153	0.299	0.053	-0.069	0.048	0.150	-0.079
CRS-R: Parent Rating: Inattentive	S* 0.046	0.027	0.090	0.064	-0.030	0.039	0.448	-0.036	S* 0.046	0.027	0.087	0.065	0.112	0.138	0.417	0.036	-0.048	0.043	0.265	-0.053
CRS-R: Teacher Rating: Inattentive	0.002	0.036	0.946	0.003	0.001	0.057	0.991	0.001	0.001	0.036	0.976	0.001	S* 0.342	0.196	0.081	0.089	-0.045	0.061	0.466	-0.041
BRIEF Parent Rating: Behavior Regulation	0.000	0.050	0.994	0.000	S 0.157	0.072	0.030 *	0.103	0.000	0.050	0.995	0.000	0.128	0.255	0.615	0.023	0.159	0.078	0.042 *	0.097
BRIEF Teacher Rating: Behavior Regulation	0.049	0.060	0.421	0.033	-0.008	0.093	0.931	-0.005	0.045	0.060	0.453	0.031	0.474	0.325	0.145	0.075	-0.070	0.101	0.492	-0.038
Tics (lower = better)																				
Motor tics (current): Assessor Rating	0.012	0.013	0.361	1.213	0.055	0.027	0.043 *	2.186	0.012	0.013	0.355	1.217	S 0.062	0.083	0.453	1.267	0.053	0.029	0.065	2.030
Phonics tics (current): Assessor Rating	-0.007	0.019	0.705	0.888	S 0.063	0.028	0.026 *	2.443	-0.007	0.019	0.698	0.886	0.108	0.088	0.218	1.513	0.057	0.029	0.053	2.137
Motor tics (current): Parent Rating	0.008	0.012	0.519	1.141	0.003	0.024	0.897	1.046	0.009	0.012	0.460	1.164	-0.032	0.085	0.710	0.886	0.006	0.027	0.813	1.087
Phonics tics (current): Parent Rating	-0.002	0.016	0.919	0.973	S* 0.040	0.024	0.088	1.780	-0.002	0.016	0.914	0.971	0.027	0.082	0.743	1.109	S* 0.042	0.026	0.099	1.754
General Intellectual Functioning																				
WASI Verbal IQ	0.060	0.059	0.308	0.034	0.008	0.086	0.924	0.004	0.062	0.059	0.291	0.035	-0.090	0.303	0.766	-0.012	0.017	0.093	0.858	0.008
WASI Performance IQ	0.004	0.067	0.955	0.002	0.145	0.098	0.137	0.068	0.005	0.067	0.938	0.003	S* 0.876	0.352	0.013 +	0.110	0.056	0.105	0.597	0.024
WASI Full Scale IQ	0.042	0.060	0.487	0.024	0.073	0.088	0.407	0.036	0.043	0.060	0.476	0.024	S* 0.362	0.314	0.249	0.048	0.038	0.095	0.691	0.017

Key: Mercury effect = Better Outcome — < .05: p-value+; >.05, <.10: p-value

Mercury effect =Worse Outcome — < .05: p-value*; >.05, <.10: p-value

P-values shown are rounded to 3 decimal places. Therefore, a value shown as 0.050 may satisify p<0.05 criterion if the original value was rounded up, or may not satisify the criterion if the value was rounded down.
S* (S) = Coefficient for males is significantly different than coefficient for females at the 0.05 (0.10) level

9.2.4. Cumulative Effects of Exposures Spanning the Prenatal Period Though Age 7 Months

9.2.4.1. Introduction

The analyses summarized in this section present the results of two additional hypothesis tests conducted to evaluate the combined effects of prenatal and postnatal exposures. The first is a joint test for additive effects of prenatal and postnatal exposure, and the second is an interaction test. The first simply tests the joint hypothesis that both effects are zero. This is done to guard against the possibility that prenatal or postnatal exposure effects are obscured by correlated errors of estimate. Because we are concerned with the cumulative effect, we only use this test when the two estimated effects are in the same direction (i.e., both prenatal and postnatal estimates are in the direction of harm, or both are in the direction of benefit). The second is a test for an interaction effect of prenatal and postnatal exposure. This test was motivated by a theory that prenatal exposure could exacerbate the effects of postnatal exposure.

The models producing the two additional hypothesis tests were fit to three sets of data. The first set was comprised of the entire sample of 1,047 assessed children. The second was a subset comprised only of data from females (n=538), and the third was the subset comprised only of males (n=509).

9.2.4.2. Model Specifications for Two Additional Hypothesis Tests

Joint Test

The first of the two tests is a test of the joint hypothesis that the effects of prenatal exposure and cumulative exposures from birth through seven months are both zero. The model is the same as model (1), presented in Section 9.2.2.2., but with an additional hypothesis as specified below. Because we are concerned with cumulative effects, this test is conducted only when coefficients for *PreNatThimer* and *Exp07mos* have the same sign (i.e., both are positive or both are negative). We used an F-test for linear regressions, and a likelihood ratio test for outcomes where logistic regression models were used to obtain estimates of the effects on binary outcomes.

$$Y = \beta_0 + \beta_1 preNatThimer + \beta_2 Exp07mos + \sum_j \alpha_j oe_j + \sum_k \alpha_{j+k} cf_k + \sum_l \alpha_{j+k+l} St_l + \varepsilon$$

$$H_0 : \begin{bmatrix} \beta_1 \\ \beta_2 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix} \quad vs \quad H_a : \begin{bmatrix} \beta_1 \\ \beta_2 \end{bmatrix} \neq \begin{bmatrix} 0 \\ 0 \end{bmatrix}$$

Interaction Model

This model produces a test of whether there is an interaction effect of *PreNatThimer* and *Exp07mos* that goes above and beyond the additive effects of the two terms.

$$Y = \beta_0 + \beta_1 preNatThimer + \beta_2 Exp07mos + \beta_3 preNatThimer * Exp07mos + \sum_j \alpha_j oe_j + \sum_k \alpha_{j+k} cf_k + \sum_l \alpha_{j+k+l} St_l + \varepsilon$$

$$H_0 : \beta_3 = 0 \quad vs \quad H_a : \beta_3 \neq 0$$

9.2.4.3. Results

A summary of models fit to the full data set is shown in Exhibit 9.2.4.1. Summaries of models fit to the subsets of data from females, and males are shown in Exhibits 9.2.4.2 and 9.4.2.3, respectively.

9.2.4.3.1. Joint Test for Additive Effect

The test for a cumulative effect makes sense only when the direction of the effect for *PreNatThimer* is consistent with the direction of the *Exp07mos* effect (i.e., coefficients for both are negative or coefficients for both are positive). When both are in a consistent direction, it is possible to find that a small, statistically non-significant effect of *PreNatThimer* can combine with a small, statistically non-significant effect of *Exp07mos* to result in a statistically significant combined effect of both. When the directions of the two effects are not consistent (e.g., *PreNatThimer* weakly associated with better outcome scores, and *Exp07mos* weakly associated with worse outcome scores) it makes no sense to conduct a joint test of a combined additive effect for both.

Full Data Set

Of the 42 outcome measures, there were 13 for which the effects of *PreNatThimer* and *Exp07mos* were in a consistent direction. For five outcomes the effects were in the direction of worse outcomes and for eight the effects were in the direction of better outcomes.

For the following five outcome measures, both the coefficients for of *PreNatThimer* and *Exp07mos* were in the direction of increased exposure being related to ***worse*** outcomes:

- NEPSY: Comprehension of instructions
- CVLT-C Free Recall, Short Delay
- CVLT-C Cued Recall, Short Delay
- CRS-R: Parent Rating: Hyperactive / impulsive
- Motor tics (current): Assessor rating

For the following eight outcome measures, both the coefficients for of *PreNatThimer* and *Exp07mos* were in the direction of increased exposure being related to ***better*** outcomes:

- Boston Naming Test
- NEPSY: Speeded Naming
- CVLT-C Cued Recall, Long Delay
- WJIII: Letter- Word Identification
- Grooved Pegboard: Dominant hand (lower=better)

- Grooved Pegboard: Non-Dominant hand (lower=better)
- Stanford Binet: Copying
- WASI Full Scale IQ

The joint hypothesis test was conducted for the 13 outcome measures listed above. Only one test was significant at the $p<0.05$ level. For the outcome measure, *Grooved Pegboard: Non-dominant Hand*, the weak prenatal effect combined with the stronger postnatal effect to result in a significant combined effect ($p=0.02$ for the hypothesis that both effects are zero). This effect was in the direction of higher exposure to ethylmercury from thimerosal being associated with lower response times (better scores) on the test.

Models Fit to Data from Females Only

For females, 21 of the 42 outcome measures had *PreNatThimer* and *Exp07mos* effects that were both in the same direction. For 14 of the outcome measures both estimates were in the direction of benefit, and for the remaining 7 outcome measures both estimates were in the direction of harm. None of the joint tests were statistically significant.

Models Fit to Data from Males Only

For males, 16 of the 42 outcome measures had *PreNatThimer* and *Exp07mos* effects that were both in the same direction. For 10 of the outcome measures both estimates were in the direction of benefit, and for the remaining 6 outcome measures both estimates were in the direction of harm. Two of the joint tests were significant at the $p<0.05$ level. For the outcome measure, *WJIII Letter Word Identification*, the weak prenatal effect combined with the stronger postnatal effect to result in a significant combined effect ($p=0.03$ for the hypothesis that both effects are zero). This effect was in the direction of higher exposure to ethylmercury from thimerosal being associated with better scores on the test. For the outcome measure, *Grooved Pegboard Dominant Hand*, the weak postnatal effect combined with the stronger prenatal effect to result in a significant combined effect ($p=0.045$ for the hypothesis that both effects are zero). This effect was in the direction of higher exposure to ethylmercury from thimerosal being associated with better scores on the test.

Exhibit 9.2.4.1. Summary of Models Testing Effects of Cumulative Exposure Prenatal Through Seven Months–Full Data Set (n=1,047)

	Model w/ Joint Test									Interaction Model: Prenatal by Postnatal								
	PreNatThimer				Exp07mos				Joint	PreNatThimer			Exp07mos			PreNatThimer X Exp07mos		
Test	Est	S.E.	P	StCf	Est	S.E.	P	StCf	Test	Est	S.E.	P	Est	S.E.	P	Est	S.E.	P
Speech and Language																		
Boston Naming Test	0.032	0.022	0.143	0.033	0.050	0.030	0.096	0.045	0.078	0.092	0.087	0.294	0.054	0.031	0.077	-0.003	0.004	0.477
NEPSY: Speeded Naming	0.057	0.027	0.034+	0.058	0.010	0.038	0.784	0.009	0.100	0.281	0.109	0.010+	0.026	0.039	0.504	-0.010	0.005	0.034*
NEPSY: Comprehension of Instructions	-0.002	0.010	0.860	-0.005	-0.014	0.014	0.310	-0.035	0.583	-0.012	0.039	0.758	-0.015	0.014	0.295	0.000	0.002	0.785
CELF: Formulated Sentences	0.021	0.021	0.327	0.026	-0.035	0.030	0.237	-0.038	.	0.042	0.085	0.621	-0.034	0.030	0.267	-0.001	0.004	0.795
CELF: Recalling Sentences	0.058	0.044	0.187	0.034	-0.001	0.062	0.984	-0.001	.	0.169	0.178	0.341	0.006	0.063	0.922	-0.005	0.007	0.520
GFTA: Articulation (lower = better)	-0.002	0.007	0.804	-0.007	0.011	0.010	0.249	0.042	.	-0.033	0.027	0.229	0.009	0.010	0.365	0.001	0.001	0.238
Stuttering: Assessor Rating (lower = better)	-0.002	0.021	0.907	0.959	0.026	0.033	0.434	1.443	.	0.068	0.097	0.482	0.030	0.033	0.361	-0.003	0.005	0.477
Stuttering: Parent Rating (lower = better)	-0.024	0.048	0.616	0.668	0.020	0.043	0.644	1.327	.	-0.033	0.158	0.836	0.019	0.044	0.659	0.000	0.007	0.955
Stuttering: Teacher Rating (lower = better)	-0.042	0.030	0.160	0.500	0.011	0.025	0.674	1.163	.	-0.011	0.094	0.905	0.012	0.026	0.629	-0.001	0.004	0.741
Verbal Memory																		
CVLT-C: Free Recall, No Delay	0.029	0.033	0.385	0.024	-0.001	0.046	0.975	-0.001	.	0.094	0.134	0.484	0.003	0.047	0.950	-0.003	0.006	0.616
CVLT-C: Free Recall, Short Delay	-0.001	0.009	0.887	-0.004	-0.024	0.013	0.066	-0.063	0.181	0.016	0.038	0.663	-0.023	0.013	0.087	-0.001	0.002	0.626
CVLT-C: Cued Recall, Short Delay	-0.001	0.008	0.910	-0.003	-0.005	0.011	0.639	-0.016	0.888	-0.001	0.033	0.975	-0.005	0.012	0.644	0.000	0.001	0.997
CVLT-C: Free Recall, Long Delay	0.001	0.009	0.917	0.003	-0.019	0.012	0.108	-0.054	.	0.040	0.035	0.248	-0.017	0.012	0.175	-0.002	0.001	0.244
CVLT-C: Cued Recall, Long Delay	0.005	0.008	0.568	0.016	0.001	0.012	0.928	0.003	0.844	0.023	0.034	0.507	0.002	0.012	0.849	-0.001	0.001	0.589
CMS Stories 1: Immediate Recall	0.024	0.042	0.570	0.013	-0.030	0.060	0.610	-0.014	.	0.254	0.169	0.134	-0.014	0.061	0.816	-0.010	0.007	0.161
CMS Stories 2: Delayed Recall	-0.010	0.041	0.817	-0.005	0.005	0.059	0.936	0.002	.	0.258	0.167	0.123	0.023	0.060	0.702	-0.012	0.007	0.099
Achievement																		
WJIII: Letter- Word Identification	0.011	0.026	0.675	0.010	0.062	0.037	0.094	0.047	0.220	0.071	0.106	0.503	0.066	0.038	0.080	-0.003	0.004	0.559
Fine Motor Coordination																		
Grooved Pegboard: Dominant Hand (lower = better)	-0.109	0.064	0.089	-0.033	-0.080	0.089	0.371	-0.021	0.149	-0.141	0.259	0.587	-0.082	0.091	0.367	0.001	0.011	0.899
Grooved Pegboard: Non-dom Hand (lower = better)	-0.083	0.077	0.284	-0.022	-0.274	0.109	0.012+	-0.062	0.022+	-0.336	0.315	0.286	-0.291	0.111	0.009 +	0.011	0.013	0.407
Finger Tapping: Dominant Hand	-0.015	0.022	0.502	-0.018	0.034	0.031	0.271	0.036	.	-0.063	0.089	0.477	0.031	0.032	0.330	0.002	0.004	0.574
Finger Tapping: Non-dominant Hand	-0.015	0.020	0.455	-0.020	0.018	0.028	0.524	0.020	.	-0.056	0.080	0.482	0.015	0.029	0.604	0.002	0.003	0.593
Visual Spatial Ability																		
Stanford Binet: Copying	0.005	0.011	0.628	0.014	0.007	0.015	0.667	0.016	0.804	0.094	0.043	0.030+	0.013	0.015	0.406	-0.004	0.002	0.035*
Attention/Executive Functioning																		
GDS Vigilance Task: Correct Responses	-0.013	0.018	0.470	-0.021	0.032	0.026	0.209	0.045	.	-0.032	0.074	0.663	0.031	0.026	0.237	0.001	0.003	0.791
GDS Vigilance Task: Errors (lower = better)	0.033	0.047	0.489	0.020	-0.022	0.067	0.742	-0.012	.	-0.036	0.191	0.852	-0.027	0.068	0.694	0.003	0.008	0.713
WISC III: Digit Span, Forward Recall	0.000	0.007	0.983	0.001	-0.002	0.010	0.820	-0.008	.	-0.018	0.027	0.511	-0.003	0.010	0.722	0.001	0.001	0.494
WISC III: Digit Span, Backward Recall	-0.013	0.006	0.027*	-0.066	0.018	0.008	0.028 +	0.078	.	-0.057	0.024	0.016*	0.015	0.008	0.070	0.002	0.001	0.055
WISC III: Digit Span, Combined	-0.012	0.010	0.244	-0.034	0.017	0.015	0.242	0.041	.	-0.069	0.042	0.097	0.013	0.015	0.372	0.002	0.002	0.157
BRIEF Parent Rating: Metacognition (lower = better)	0.021	0.066	0.744	0.010	-0.052	0.092	0.573	-0.020	.	-0.068	0.266	0.800	-0.058	0.094	0.535	0.004	0.011	0.730
BRIEF Teacher Rating: Metacognition (lower = better)	0.026	0.088	0.764	0.010	-0.147	0.133	0.268	-0.046	.	-0.571	0.357	0.110	-0.193	0.135	0.154	0.025	0.015	0.085
Behavior Regulation (lower = better)																		
CRS-R: Parent Rating: Hyperactive/Impulsive	0.007	0.019	0.725	0.011	0.019	0.026	0.469	0.026	0.717	-0.103	0.074	0.168	0.012	0.026	0.659	0.005	0.003	0.130
CRS-R: Teacher Rating: Hyperactive/Impulsive	0.023	0.022	0.301	0.033	-0.048	0.034	0.157	-0.059	.	-0.219	0.090	0.015+	-0.066	0.034	0.054	0.010	0.004	0.006*
CRS-R: Parent Rating: Inattentive	0.011	0.022	0.606	0.016	-0.024	0.030	0.433	-0.028	.	0.068	0.087	0.438	-0.020	0.031	0.524	-0.002	0.004	0.504
CRS-R: Teacher Rating: Inattentive	0.002	0.029	0.939	0.002	-0.034	0.043	0.432	-0.033	.	-0.200	0.116	0.086	-0.050	0.044	0.260	0.009	0.005	0.074
BRIEF Parent Rating: Behavior Regulation	-0.021	0.040	0.594	-0.016	0.077	0.055	0.167	0.050	.	-0.249	0.160	0.119	0.061	0.056	0.278	0.010	0.007	0.141
BRIEF Teacher Rating: Behavior Regulation	0.035	0.048	0.455	0.024	-0.045	0.072	0.535	-0.026	.	-0.249	0.192	0.195	-0.066	0.073	0.367	0.012	0.008	0.127
Tics (lower = better)																		
Motor tics (current): Assessor Rating	0.017	0.011	0.104	1.336	0.032	0.022	0.142	1.586	0.326	0.121	0.051	0.017 *	0.040	0.022	0.070	-0.004	0.002	0.046+
Phonics tics (current): Assessor Rating	-0.011	0.018	0.560	0.839	0.037	0.023	0.102	1.702	.	0.066	0.073	0.362	0.042	0.023	0.070	-0.004	0.004	0.305
Motor tics (current): Parent Rating	0.003	0.012	0.832	1.043	-0.001	0.021	0.963	0.986	.	0.021	0.054	0.700	0.000	0.021	0.990	-0.001	0.002	0.732
Phonics tics (current): Parent Rating	-0.014	0.016	0.409	0.798	0.007	0.019	0.699	1.109	.	0.048	0.061	0.428	0.011	0.019	0.556	-0.003	0.003	0.317
General Intellectual Functioning																		
WASI Verbal IQ	0.054	0.047	0.252	0.030	-0.044	0.066	0.506	-0.021	.	0.136	0.189	0.472	-0.038	0.067	0.571	-0.004	0.008	0.652
WASI Performance IQ	-0.008	0.054	0.881	-0.004	0.130	0.074	0.080	0.061	.	0.303	0.224	0.177	0.151	0.076	0.046+	-0.014	0.010	0.153
WASI Full Scale IQ	0.026	0.048	0.594	0.015	0.059	0.068	0.383	0.029	0.584	0.244	0.201	0.226	0.074	0.069	0.284	-0.010	0.009	0.265

Key: Mercury effect = Better Outcome — < .05: p-value+; >.05, <.10: p-value

Mercury effect =Worse Outcome — < .05: p-value*; >.05, <.10: p-value

P-values shown are rounded to 3 decimal places. Therefore, a value shown as 0.050 may satisfy p<0.05 criterion if the original value was rounded up, or may not satisfy the criterion if the value was rounded down.

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Exhibit 9.2.4.2. Summary of Models Testing Effects of Cumulative Exposure Prenatal Through Seven Months – Females (n=538)

	Model w/ Joint Test									Interaction Model: Prenatal by Postnatal								
	PreNatThimer				Exp07mos				Joint	PreNatThimer			Exp07mos			PreNatThimer X Exp07mos		
Test	Est	S.E.	P	StCf	Est	S.E.	P	StCf	Test	Est	S.E.	P	Est	S.E.	P	Est	S.E.	P
Speech and Language																		
Boston Naming Test	0.037	0.036	0.303	0.039	0.053	0.045	0.240	0.048	0.294	0.139	0.137	0.310	0.060	0.046	0.192	-0.004	0.006	0.441
NEPSY: Speeded Naming	0.041	0.042	0.337	0.042	0.018	0.054	0.738	0.016	0.595	0.269	0.160	0.093	0.035	0.055	0.523	-0.010	0.006	0.139
NEPSY: Comprehension of Instructions	0.007	0.016	0.658	0.021	-0.005	0.020	0.815	-0.012	.	-0.005	0.060	0.938	-0.006	0.021	0.786	0.000	0.002	0.840
CELF: Formulated Sentences	0.035	0.032	0.273	0.043	-0.022	0.040	0.593	-0.023	.	0.097	0.121	0.424	-0.017	0.041	0.681	-0.003	0.005	0.598
CELF: Recalling Sentences	0.060	0.072	0.403	0.035	0.025	0.090	0.780	0.013	0.677	0.212	0.271	0.433	0.036	0.092	0.693	-0.006	0.011	0.560
GFTA: Articulation (lower = better)	-0.006	0.011	0.547	-0.029	0.007	0.014	0.600	0.027	.	-0.048	0.040	0.237	0.004	0.014	0.778	0.002	0.002	0.289
Stuttering: Assessor Rating (lower = better)	0.043	0.025	0.086	2.033	0.043	0.059	0.467	1.839	0.760	0.293	0.151	0.052	0.066	0.061	0.285	-0.011	0.007	0.124
Stuttering: Parent Rating (lower = better)	-0.712	8.358	0.932	0.000	0.096	0.080	0.230	3.927	.	-0.529	13.692	0.969	0.096	0.080	0.230	-0.001	0.571	0.998
Stuttering: Teacher Rating (lower = better)	-0.041	0.050	0.410	0.503	-0.001	0.045	0.987	0.990	1.000	-0.172	0.216	0.426	-0.005	0.045	0.904	0.005	0.007	0.509
Verbal Memory																		
CVLT-C: Free Recall, No Delay	0.017	0.053	0.752	0.014	-0.008	0.066	0.907	-0.006	.	0.170	0.200	0.397	0.004	0.068	0.955	-0.006	0.008	0.428
CVLT-C: Free Recall, Short Delay	-0.004	0.015	0.793	-0.012	-0.031	0.018	0.091	-0.082	0.232	0.058	0.056	0.304	-0.026	0.019	0.165	-0.003	0.002	0.255
CVLT-C: Cued Recall, Short Delay	-0.012	0.012	0.336	-0.041	-0.013	0.015	0.387	-0.040	0.432	0.014	0.046	0.756	-0.011	0.016	0.475	-0.001	0.002	0.557
CVLT-C: Free Recall, Long Delay	-0.010	0.013	0.446	-0.033	-0.022	0.017	0.190	-0.061	0.320	0.099	0.050	0.047+	-0.013	0.017	0.435	-0.005	0.002	0.023*
CVLT-C: Cued Recall, Long Delay	-0.010	0.012	0.412	-0.034	0.003	0.016	0.841	0.009	.	0.039	0.047	0.413	0.007	0.016	0.675	-0.002	0.002	0.283
CMS Stories 1: Immediate Recall	0.003	0.067	0.964	0.002	0.071	0.084	0.400	0.032	0.701	0.162	0.252	0.520	0.083	0.086	0.337	-0.007	0.010	0.513
CMS Stories 2: Delayed Recall	-0.049	0.065	0.451	-0.027	0.092	0.083	0.268	0.043	.	0.108	0.245	0.659	0.103	0.085	0.221	-0.007	0.010	0.506
Achievement																		
WJIII: Letter- Word Identification	-0.031	0.042	0.452	-0.028	-0.015	0.053	0.776	-0.012	0.724	0.060	0.158	0.706	-0.008	0.054	0.879	-0.004	0.006	0.551
Fine Motor Coordination																		
Grooved Pegboard: Dominant Hand (lower = better)	-0.070	0.108	0.515	-0.021	-0.064	0.134	0.631	-0.017	0.722	-0.099	0.407	0.809	-0.066	0.137	0.628	0.001	0.017	0.943
Grooved Pegboard: Non-dom Hand (lower = better)	-0.037	0.127	0.771	-0.010	-0.308	0.161	0.056	-0.070	0.155	-0.375	0.478	0.433	-0.334	0.165	0.043+	0.014	0.019	0.464
Finger Tapping: Dominant Hand	0.004	0.034	0.899	0.005	-0.005	0.043	0.903	-0.006	.	0.004	0.129	0.978	-0.005	0.044	0.904	0.000	0.005	0.995
Finger Tapping: Non-dominant Hand	0.022	0.030	0.468	0.029	-0.024	0.039	0.532	-0.028	.	-0.024	0.115	0.833	-0.028	0.040	0.484	0.002	0.005	0.676
Visual Spatial Ability																		
Stanford Binet: Copying	-0.039	0.018	0.026*	-0.110	0.016	0.022	0.480	0.038	.	0.050	0.066	0.452	0.023	0.023	0.324	-0.004	0.003	0.163
Attention/Executive Functioning																		
GDS Vigilance Task: Correct Responses	-0.018	0.028	0.515	-0.030	0.046	0.036	0.195	0.064	.	-0.048	0.106	0.652	0.044	0.037	0.230	0.001	0.004	0.773
GDS Vigilance Task: Errors (lower = better)	0.023	0.057	0.685	0.014	-0.123	0.072	0.090	-0.066	.	-0.104	0.214	0.627	-0.132	0.074	0.074	0.005	0.009	0.538
WISC III: Digit Span, Forward Recall	-0.015	0.011	0.195	-0.065	-0.008	0.014	0.578	-0.030	0.368	-0.009	0.043	0.835	-0.008	0.015	0.606	0.000	0.002	0.890
WISC III: Digit Span, Backward Recall	-0.004	0.009	0.684	-0.020	0.026	0.012	0.025+	0.115	.	-0.032	0.036	0.376	0.024	0.012	0.044+	0.001	0.001	0.420
WISC III: Digit Span, Combined	-0.019	0.017	0.254	-0.054	0.023	0.021	0.265	0.057	.	-0.053	0.064	0.407	0.021	0.022	0.329	0.001	0.003	0.583
BRIEF Parent Rating: Metacognition (lower = better)	-0.159	0.102	0.120	-0.073	-0.084	0.126	0.506	-0.033	0.241	-0.633	0.385	0.101	-0.121	0.129	0.352	0.020	0.016	0.202
BRIEF Teacher Rating: Metacognition (lower = better)	-0.043	0.133	0.745	-0.016	-0.011	0.181	0.952	-0.003	0.947	-0.663	0.524	0.206	-0.073	0.188	0.699	0.025	0.021	0.222
Behavior Regulation (lower = better)																		
CRS-R: Parent Rating: Hyperactive/Impulsive	-0.020	0.029	0.475	-0.033	-0.030	0.036	0.402	-0.042	0.547	-0.092	0.107	0.391	-0.036	0.037	0.336	0.003	0.004	0.489
CRS-R: Teacher Rating: Hyperactive/Impulsive	0.008	0.029	0.779	0.012	-0.051	0.039	0.193	-0.063	.	-0.028	0.114	0.805	-0.055	0.041	0.180	0.001	0.004	0.742
CRS-R: Parent Rating: Inattentive	-0.048	0.032	0.139	-0.067	-0.020	0.040	0.627	-0.023	0.300	-0.132	0.121	0.276	-0.026	0.041	0.525	0.004	0.005	0.469
CRS-R: Teacher Rating: Inattentive	-0.001	0.041	0.989	-0.001	-0.048	0.056	0.391	-0.046	0.692	-0.169	0.162	0.296	-0.064	0.058	0.266	0.007	0.006	0.281
BRIEF Parent Rating: Behavior Regulation	-0.058	0.062	0.349	-0.044	-0.044	0.077	0.566	-0.029	0.549	-0.386	0.231	0.095	-0.070	0.079	0.379	0.014	0.009	0.141
BRIEF Teacher Rating: Behavior Regulation	0.037	0.070	0.596	0.026	-0.019	0.096	0.839	-0.012	.	-0.087	0.274	0.750	-0.031	0.099	0.752	0.005	0.011	0.639
Tics (lower = better)																		
Motor tics (current): Assessor Rating	0.041	0.022	0.065	1.972	0.019	0.038	0.619	1.306	0.882	0.244	0.112	0.029*	0.036	0.039	0.350	-0.010	0.006	0.089
Phonics tics (current): Assessor Rating	-0.018	0.044	0.688	0.747	0.039	0.039	0.316	1.757	.	0.065	0.192	0.734	0.042	0.040	0.291	-0.004	0.009	0.675
Motor tics (current): Parent Rating	-0.064	0.059	0.277	0.344	0.010	0.041	0.800	1.159	.	0.211	0.191	0.270	0.022	0.042	0.595	-0.014	0.010	0.182
Phonics tics (current): Parent Rating	-0.102	0.063	0.107	0.184	-0.035	0.035	0.321	0.609	0.614	0.198	0.170	0.244	-0.022	0.036	0.544	-0.017	0.010	0.097
General Intellectual Functioning																		
WASI Verbal IQ	0.021	0.076	0.788	0.012	-0.087	0.096	0.363	-0.043	.	-0.089	0.287	0.756	-0.095	0.098	0.332	0.005	0.012	0.691
WASI Performance IQ	-0.034	0.086	0.696	-0.018	0.129	0.102	0.206	0.060	.	0.028	0.342	0.935	0.134	0.105	0.203	-0.003	0.015	0.852
WASI Full Scale IQ	-0.022	0.079	0.785	-0.012	0.079	0.097	0.415	0.039	.	-0.081	0.313	0.795	0.075	0.100	0.454	0.003	0.013	0.844

		< .05	>.05, <.10		< .05	>.05, <.10
Key: Mercury effect = Better Outcome		p-value+	p-value	Mercury effect =Worse Outcome	p-value*	p-value

P-values shown are rounded to 3 decimal places. Therefore, a value shown as 0.050 may satisfy p<0.05 criterion if the original value was rounded up, or may not satisfy the criterion if the value was rounded down.

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Exhibit 9.2.4.3. Summary of Models Testing Effects of Cumulative Exposure Prenatal Through Seven Months – Males (n=509)

	Model w/ Joint Test									Interaction Model: Prenatal by Postnatal								
	PreNatThimer				Exp07mos				Joint	PreNatThimer			Exp07mos			PreNatThimer X Exp07mos		
Test	Est	S.E.	P	StCf	Est	S.E.	P	StCf	Test	Est	S.E.	P	Est	S.E.	P	Est	S.E.	P
Speech and Language																		
Boston Naming Test	0.040	0.028	0.152	0.041	0.052	0.042	0.216	0.047	0.149	0.053	0.119	0.659	0.053	0.043	0.217	-0.001	0.005	0.910
NEPSY: Speeded Naming	0.056	0.036	0.123	0.057	0.002	0.056	0.971	0.002	0.300	0.217	0.158	0.169	0.011	0.057	0.840	-0.007	0.007	0.294
NEPSY: Comprehension of Instructions	-0.011	0.013	0.412	-0.031	-0.027	0.020	0.169	-0.069	0.253	-0.056	0.057	0.326	-0.030	0.020	0.137	0.002	0.002	0.414
CELF: Formulated Sentences	0.017	0.029	0.554	0.021	-0.045	0.045	0.314	-0.048		-0.049	0.125	0.698	-0.050	0.046	0.279	0.003	0.005	0.588
CELF: Recalling Sentences	0.065	0.059	0.272	0.038	-0.039	0.089	0.666	-0.019		0.110	0.254	0.664	-0.036	0.091	0.692	-0.002	0.011	0.854
GFTA: Articulation (lower = better)	0.002	0.009	0.802	0.010	0.018	0.014	0.182	0.070	0.390	-0.021	0.038	0.581	0.017	0.014	0.228	0.001	0.002	0.530
Stuttering: Assessor Rating (lower = better)	-0.470	1.061	0.658	0.000	0.015	0.041	0.710	1.246		-0.636	4.816	0.895	0.015	0.041	0.710	0.007	0.224	0.974
Stuttering: Parent Rating (lower = better)	-0.004	0.042	0.917	0.930	-0.019	0.054	0.729	0.767	0.943	-0.010	0.150	0.947	-0.019	0.055	0.729	0.000	0.006	0.969
Stuttering: Teacher Rating (lower = better)	-0.033	0.037	0.381	0.579	0.019	0.032	0.554	1.311		0.116	0.122	0.344	0.029	0.033	0.389	-0.008	0.007	0.242
Verbal Memory																		
CVLT-C: Free Recall, No Delay	0.026	0.044	0.554	0.022	-0.019	0.068	0.782	-0.014		0.084	0.194	0.666	-0.015	0.069	0.822	-0.003	0.008	0.761
CVLT-C: Free Recall, Short Delay	-0.005	0.013	0.688	-0.015	-0.016	0.019	0.406	-0.041	0.637	-0.023	0.054	0.674	-0.017	0.019	0.384	0.001	0.002	0.736
CVLT-C: Cued Recall, Short Delay	0.002	0.011	0.881	0.006	0.000	0.017	0.979	-0.001		-0.033	0.048	0.494	-0.002	0.017	0.888	0.002	0.002	0.460
CVLT-C: Free Recall, Long Delay	0.003	0.012	0.769	0.011	-0.019	0.018	0.305	-0.052		-0.014	0.052	0.792	-0.020	0.018	0.288	0.001	0.002	0.734
CVLT-C: Cued Recall, Long Delay	0.013	0.012	0.291	0.044	0.000	0.019	0.995	0.000	0.570	-0.007	0.054	0.899	-0.001	0.019	0.955	0.001	0.002	0.705
CMS Stories 1: Immediate Recall	0.044	0.056	0.433	0.023	-0.118	0.087	0.177	-0.054		0.285	0.239	0.234	-0.103	0.089	0.247	-0.011	0.010	0.300
CMS Stories 2: Delayed Recall	0.018	0.056	0.753	0.010	-0.054	0.087	0.533	-0.025		0.343	0.244	0.161	-0.037	0.087	0.674	-0.014	0.010	0.172
Achievement																		
WJIII: Letter- Word Identification	0.039	0.035	0.261	0.035	0.126	0.054	0.020+	0.096	0.030+	0.009	0.150	0.953	0.124	0.055	0.024+	0.001	0.006	0.834
Fine Motor Coordination																		
Grooved Pegboard: Dominant Hand (lower = better)	-0.183	0.080	0.022+	-0.055	-0.097	0.121	0.423	-0.025	0.045+	0.016	0.344	0.962	-0.086	0.122	0.481	-0.009	0.015	0.552
Grooved Pegboard: Non-dom Hand (lower = better)	-0.131	0.102	0.199	-0.034	-0.186	0.155	0.230	-0.042	0.191	0.015	0.446	0.973	-0.179	0.157	0.255	-0.006	0.019	0.737
Finger Tapping: Dominant Hand	-0.020	0.029	0.493	-0.025	0.062	0.046	0.180	0.065		-0.108	0.127	0.393	0.056	0.047	0.229	0.004	0.005	0.475
Finger Tapping: Non-dominant Hand	-0.028	0.027	0.296	-0.038	0.036	0.042	0.391	0.041		-0.038	0.117	0.746	0.036	0.043	0.406	0.000	0.005	0.934
Visual Spatial Ability																		
Stanford Binet: Copying	0.034	0.014	0.015+	0.095	-0.013	0.021	0.558	-0.030		0.099	0.061	0.103	-0.008	0.022	0.702	-0.003	0.003	0.273
Attention/Executive Functioning																		
GDS Vigilance Task: Correct Responses	-0.024	0.025	0.337	-0.039	0.022	0.039	0.573	0.030		-0.104	0.110	0.346	0.017	0.039	0.665	0.003	0.005	0.458
GDS Vigilance Task: Errors (lower = better)	0.034	0.073	0.643	0.021	-0.019	0.110	0.865	-0.010		0.228	0.317	0.472	-0.006	0.112	0.954	-0.008	0.013	0.530
WISC III: Digit Span, Forward Recall	0.011	0.009	0.198	0.050	0.001	0.013	0.949	0.003	0.433	-0.032	0.037	0.385	-0.002	0.013	0.881	0.002	0.002	0.230
WISC III: Digit Span, Backward Recall	-0.020	0.008	0.009*	-0.102	0.008	0.012	0.478	0.036		-0.071	0.033	0.033*	0.006	0.012	0.643	0.002	0.001	0.116
WISC III: Digit Span, Combined	-0.010	0.014	0.452	-0.029	0.010	0.021	0.617	0.025		-0.083	0.058	0.155	0.006	0.021	0.763	0.003	0.003	0.200
BRIEF Parent Rating: Metacognition (lower = better)	0.131	0.091	0.153	0.060	-0.020	0.140	0.885	-0.008		0.318	0.397	0.423	-0.008	0.142	0.954	-0.008	0.017	0.628
BRIEF Teacher Rating: Metacognition (lower = better)	0.117	0.125	0.352	0.043	-0.272	0.200	0.174	-0.086		-0.632	0.547	0.249	-0.311	0.201	0.124	0.032	0.023	0.161
Behavior Regulation (lower = better)																		
CRS-R: Parent Rating: Hyperactive/Impulsive	0.026	0.025	0.308	0.042	0.052	0.038	0.174	0.073	0.213	-0.109	0.109	0.316	0.045	0.039	0.247	0.006	0.005	0.202
CRS-R: Teacher Rating: Hyperactive/Impulsive	0.036	0.034	0.291	0.052	-0.058	0.056	0.303	-0.072		-0.417	0.147	0.005+	-0.082	0.056	0.144	0.020	0.006	0.002*
CRS-R: Parent Rating: Inattentive	0.043	0.031	0.158	0.061	-0.032	0.047	0.497	-0.038		0.240	0.133	0.071	-0.019	0.047	0.685	-0.009	0.006	0.129
CRS-R: Teacher Rating: Inattentive	0.006	0.042	0.888	0.007	-0.024	0.069	0.729	-0.023		-0.266	0.183	0.147	-0.040	0.070	0.571	0.012	0.008	0.128
BRIEF Parent Rating: Behavior Regulation	0.024	0.054	0.659	0.018	0.166	0.081	0.040*	0.109	0.103	-0.086	0.232	0.712	0.160	0.082	0.051	0.005	0.010	0.628
BRIEF Teacher Rating: Behavior Regulation	0.079	0.070	0.261	0.055	-0.090	0.112	0.422	-0.053		-0.397	0.301	0.188	-0.111	0.112	0.322	0.021	0.013	0.105
Tics (lower = better)																		
Motor tics (current): Assessor Rating	0.017	0.013	0.218	1.317	0.053	0.030	0.076	2.143	0.187	0.118	0.066	0.074	0.059	0.030	0.049*	-0.004	0.003	0.129
Phonics tics (current): Assessor Rating	-0.009	0.020	0.665	0.865	0.051	0.029	0.085	2.060		0.123	0.091	0.177	0.060	0.030	0.047*	-0.006	0.005	0.171
Motor tics (current): Parent Rating	0.007	0.013	0.605	1.116	-0.011	0.025	0.657	0.851		0.013	0.062	0.831	-0.011	0.026	0.676	0.000	0.003	0.913
Phonics tics (current): Parent Rating	-0.002	0.017	0.929	0.975	0.030	0.025	0.217	1.541		0.043	0.075	0.567	0.033	0.025	0.185	-0.002	0.003	0.553
General Intellectual Functioning																		
WASI Verbal IQ	0.068	0.062	0.270	0.039	-0.019	0.094	0.841	-0.009		0.279	0.267	0.297	-0.006	0.095	0.953	-0.009	0.011	0.417
WASI Performance IQ	0.024	0.071	0.733	0.013	0.111	0.110	0.311	0.052	0.548	0.460	0.308	0.136	0.139	0.111	0.213	-0.019	0.013	0.146
WASI Full Scale IQ	0.052	0.064	0.417	0.030	0.020	0.099	0.842	0.010	0.695	0.422	0.281	0.134	0.042	0.100	0.673	-0.016	0.012	0.177

Key: Mercury effect = Better Outcome — <.05 p-value+; >.05, <.10 p-value

Mercury effect =Worse Outcome — <.05 p-value*; >.05, <.10 p-value

P-values shown are rounded to 3 decimal places. Therefore, a value shown as 0.050 may satisfy p<0.05 criterion if the original value was rounded up, or may not satisfy the criterion if the value was rounded down.

9.2.4.3.2. Test of Prental-by-Postnatal Exposure Interaction Effect

Full Data Set

Among the hypothesis tests for an interaction effect conducted for the 42 outcome measures, four were significant at the $p<0.05$ level, and three additional tests fell below 0.10. If the direction of the main effects of *PreNatThimer* and *Exp07mos* had been consistent with the direction of the interaction effect (*PreNatThimer*Exp07mos*), the interpretation of a significant interaction would be straightforward. For example, if a higher score were considered a better outcome, and the coefficients for all three effects were negative, one could conclude that higher exposure was associated with a worse outcome, and that the effect of having both high prenatal and high postnatal exposure results in a negative effect above and beyond the individual additive effects of exposure during the two periods. But that kind of consistency did not occur in any of the models where the p-value for the interaction was less than 0.10. In each model there was a mix of positive and negative coefficients for the three terms.

In order to understand the complex results produced from these models, we produced plots of the values on the outcome variables that would be predicted from the models for various exposure levels. The plots show the predicted values of the outcome variable (Y), for increasing values of the exposure variables (*PreNatThimer,* and *Exp07mos*). Based on the distributions of exposures for the entire sample of girls and boys combined, we made cut-points to classify prenatal and postnatal exposures as *Very Low, Low, High,* and *Very High*. Our goal was to show the predicted value of Y for all sixteen possible combinations of the four prenatal groups (very low to very high) crossed with the four postnatal groups (very low to very high). However, for cells with no observations (e.g., there were zero children in the "high *PreNatThimer*" and "very low *Exp07mos*" group), no predicted value is shown. We picked the most extreme values of *PreNatThimer* and *Exp07mos* observed within each crossed group and plotted a set of predicted values for different postnatal exposures within each prenatal exposure category. The exposure categories used for the plots of predicted values are shown below.

	Exposure Categories			
	Very Low	Low	High	Very High
PreNatThimer (Prenatal)	0	11.25 – 12.75	25 to 25.5	50 to 100
Exp07mos (postnatal)	0 to 11.59	11.6 to 19.99	20 to 30	30.01 to 38.3
PreNatThimer is a measure of cumulative exposure to ethylmercury from vaccines and immune globulins during the prenatal period and is expressed in micrograms. *Exp07mos* is a cumulative measure of exposure to ethylmercury from vaccines and immune globulins for the period from birth through seven months of age and is expressed as micrograms of mercury divided by child's body weight at the time of receipt, summed over all receipts in the age range.				

The plot shown in Exhibit 9.2.4.4b is a hypothetical example wherein the coefficients for all three terms are negative (i.e., the terms for *PreNatThimer, Exp07mos,* and

*PreNatThimer*Exp07mos* are all in a consistent direction). This hypothetical example can be contrasted to the results from the observed data, shown later, where the coefficients for the three terms are not in a consistent direction.

The plot of the hypothetical data shows that as *PreNatThimer* increases in value, the predicted value of the outcome variable Y decreases. And as *Exp07mos* increases in value, the predicted value of the outcome variable Y decreases. It also shows that the slope of the *Exp07mos* effect is steeper for higher values of *PreNatThimer.* The plot has four panels indicated by the vertical dotted lines. The leftmost panel is for Very Low prenatal exposures. The Very Low prenatal exposure category corresponds to zero prenatal exposure, so the plots in this group use predictions with PreNatThimer = 0, as indicated in the first row of numbers at the bottom of the plot. The Exp07mos values used are shown in the second row of numbers at the bottom of the plot. We used the low point of the range for the two lower postnatal exposure categories (0 for Very Low and 11.6 for Low) and the high point of the range for the higher exposure categories (30 for High and 42 for Very High). The plotting symbols (open circles) in this panel show the predicted values of Y when *PreNatThimer* is equal to zero, and *Exp07mos* is at values 0, 11.6, 30, and 42. In this example there is a slight downward slope associated with increasing values of *Exp07mos* when the value of *PreNatThimer* is held constant at zero. The third row of numbers shown along the bottom of the plot is labeled "n in group". This hypothetical example used the observed numbers in each exposure group. For example, there were 106 children that had zero prenatal exposure and were in the *very low* group for *Exp07mos*.

Exhibits 9.2.4.5 through 9.2.4.8 show the estimates and plots for four outcome measures that had significant interaction effect at the 0.05 level in the models fit to the full data set. Exhibits 9.2.4.9 and 9.2.4.10 correspond to the one significant interaction effect for females and the one significant interaction effect for males.

Exhibit 9.2.4.5a is a summary of results from the interaction model for the NEPSY Speeded Naming outcome measure. The summary shows the estimates (regression coefficients) and their standard errors and p-values for the thimerosal exposure variables. For the sake of brevity, the estimates for the intercept term and all of the covariates are omitted from the summary. For this particular outcome measure, a higher score is better. The coefficients for the *PreNatThimer* and *Exp07mos* terms are positive, and the coefficient for the interaction term (*PreNatThimer* * *Exp07mos*) is negative. The p-value for the interaction is below 0.05, indicating a statistically significant interaction effect. The coefficient for the *PreNatThimer* term is large, relative to its standard error, and positive, suggesting that, holding postnatal exposure constant at zero, one would expect that higher prenatal exposures would be related to more desirable scores on the outcome measure.

The estimated main effects from the model without the (*PreNatThimer*Exp07mos*) interaction are shown in Exhibit 9.2.4.5b . Comparing Exhibits 9.2.4.5a and 9.2.4.5b, it is evident that the addition of the interaction term substantially increased the size of the

estimated positive coefficients for both main effects, with an offsetting negative interaction.

Plots of predicted values from the interaction model are shown in Exhibit 9.2.4.5c. The left-most panel of the plot shows that when *PreNatThimer* is held constant at zero, increases in the value of *Exp07mos* have a very weak positive association with the outcome measure. In this portion of the plot, as the values of *Exp07mos* increase, the predicted values of Y increase a small amount. Note that, by far, most children had zero prenatal thimerosal exposure, so the left-most panel of the plot represents the data for roughly 90 percent of the children in the sample. The next panel to the right shows the predicted values of Y when *PreNatThimer* is equal to 11.25, for several increasing values of *Exp07mos*. The plot shows that when *Exp07mos* is at very low or low values, the model predicts that 11.25 micrograms of prenatal exposure is associated with better outcome scores than are predicted when prenatal exposure is zero, and postnatal exposure is at any value, low or high. When postnatal cumulative exposure is at high or very high levels, the predicted benefit of 11.25 micrograms of prenatal exposure diminishes to near zero. The predicted values of Y when *PreNatThimer* is 11.25, and *Exp07mos* is high or very high are very close to the predicted values of Y when *PreNatThimer* is zero. The two right-most panels of the exhibit tell a very similar story. The predicted benefits of higher prenatal exposure diminish to near zero as postnatal exposure increases.

For *Stanford Binet Copying* and *CRS-R Teacher Rated Hyperactive/Impulsive* outcome measures (Exhibits 9.2.4.6 and 9.2.4.7), the models predict beneficial effects of postnatal exposure when prenatal exposure is zero, and harmful effects when both prenatal and postnatal exposures are high, but at the lower levels postnatal exposure, the predicted benefits of high or very high prenatal exposure are large.

When there is zero prental exposure, the model for *Assessor Rated Motor Tics* (Exhibit 9.2.4.8) predicts that the risk of tics with increases with increasing postnatal exposure, but when there is prenatal exposure, increasing postnatal exposure is associated with decreased risk of tics.

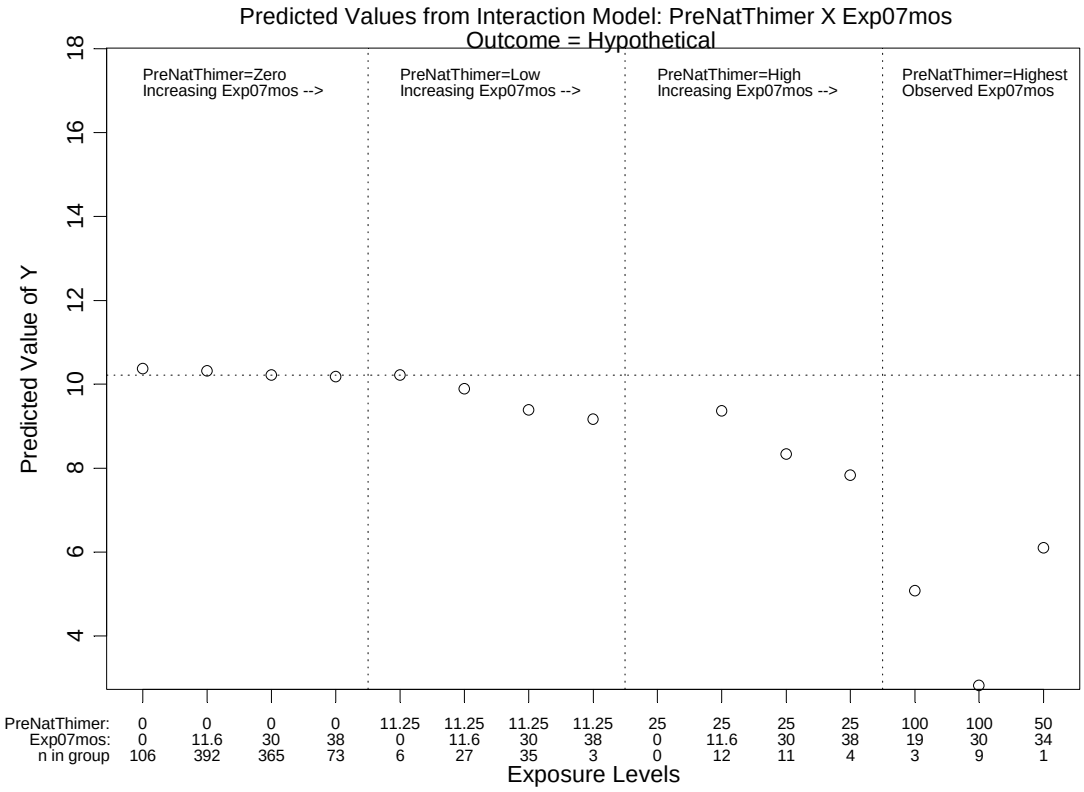
For females, the predicted beneficial effects of high prenatal exposure on the *CVLT-C Free Recall Long Delay* outcome measure are similar in magnitude to the predicted harmful effects of having both high prenatal and high postnatal exposure (Exhibit 9.2.4.9). The results for males on *CRS-R Teacher Rated Hyperactive/Impulsive* outcome (Exhibit 9.2.4.10) are very similar to the previously displayed results on the same outcome measure for the full data set (Exhibit 9.2.4.7).

None of the significant interaction effects suggest clear evidence of either harm or benefit associated with the interaction between prenatal and postnatal exposure.

Exhibit 9.2.4.4a. Hypothetical Example Where Coefficients for PreNatThimer, Exp07mos, and the Interaction of PreNatThimer by Exp07mos are all Negative
Summary of Regression Coefficients from Interaction Model

Variable Name	Estimate	Standard Error	P-Value
PreNatThimer	-0.014		
Exp07mos	-.005		
PreNatThimer*Exp07mos	-0.002		

Exhibit 9.2.4.4b. Hypothetical Example Where Coefficients for PreNatThimer, Exp07mos, and the Interaction of PreNatThimer by Exp07mos are all Negative
Plot of Predicted Values of Y



Notes: Plot symbol indicates predicted value of Y when the values if *PreNatThimer* and *Exp07mos* are equal to the values shown below the x-axis. For example, the left-most plotting symbol shows the predicted value of Y when *PreNatThimer* = 0 and *Exp07mos* = 0. The next symbol to the right shows the predicted value when *PreNatThimer* = 0 and *Exp07mos* = 11.6, and so on.

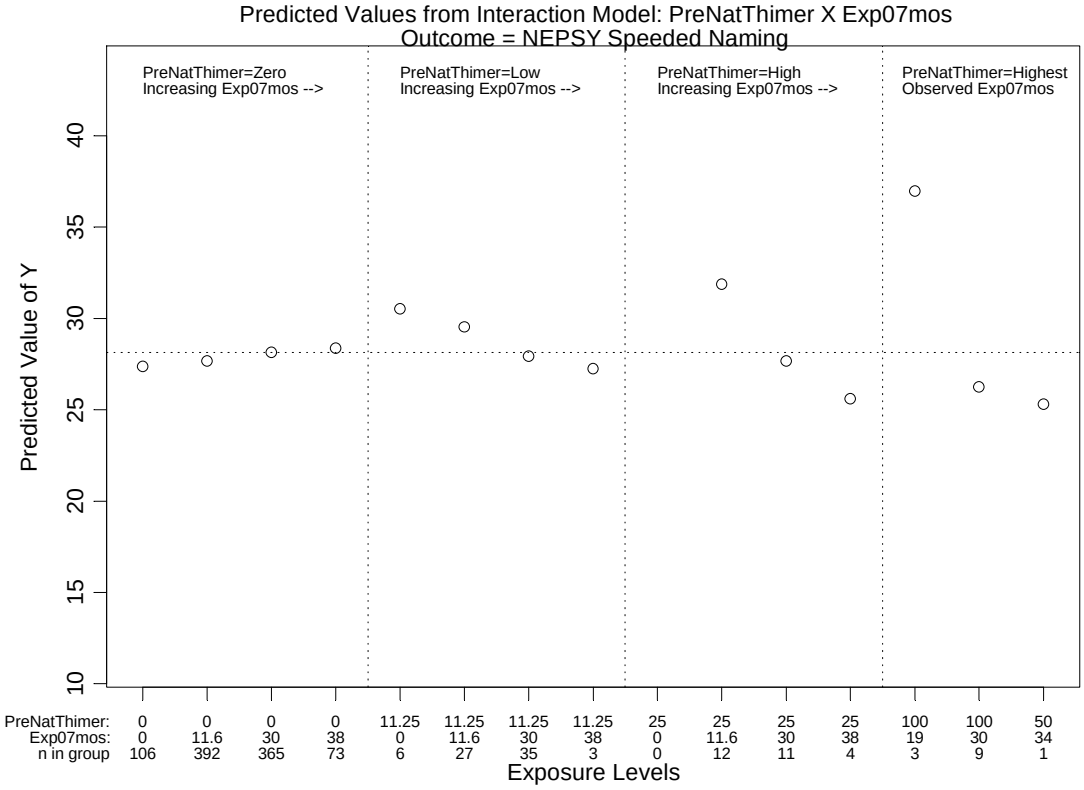
Exhibit 9.2.4.5a. NEPSY Speeded Naming
Summary of Regression Coefficients from Interaction Model

Variable Name	Estimate	Standard Error	P-Value
PreNatThimer	0.281	0.109	0.010
Exp07mos	0.026	0.039	0.504
PreNatThimer*Exp07mos	-0.010	0.005	0.034

Exhibit 9.2.4.5b. NEPSY Speeded Naming
Summary of Regression Coefficients from Model Without The Interaction

Variable Name	Estimate	Standard Error	P-Value
PreNatThimer	0.057	0.027	0.034
Exp07mos	0.010	0.038	0.784

Exhibit 9.2.4.5c. NEPSY Speeded Naming
Plot of Predicted Values of Y



Notes: Plot symbol indicates predicted value of Y when the values if *PreNatThimer* and *Exp07mos* are equal to the values shown below the x-axis. For example, the left-most plotting symbol shows the predicted value of Y when *PreNatThimer* = 0 and *Exp07mos* = 0. The next symbol to the right shows the predicted value when *PreNatThimer* = 0 and *Exp07mos* = 11.6, and so on.

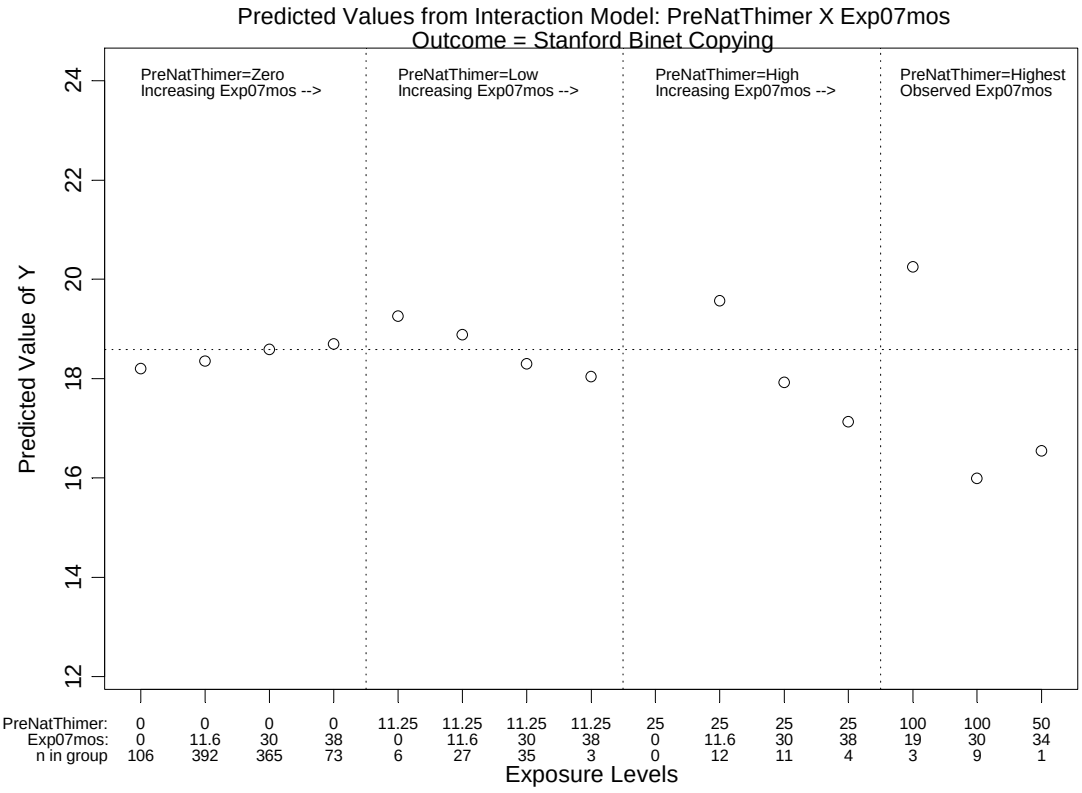
Exhibit 9.2.4.6a. Stanford Binet: Copying
Summary of Regression Coefficients from Interaction Model

Variable Name	Estimate	Standard Error	P-Value
PreNatThimer	0.094	0.043	0.030
Exp07mos	0.013	0.015	0.406
PreNatThimer*Exp07mos	-0.004	0.002	0.035

Exhibit 9.2.4.6b. Stanford Binet: Copying
Summary of Regression Coefficients from Model Without Interaction

Variable Name	Estimate	Standard Error	P-Value
PreNatThimer	0.005	0.011	0.628
Exp07mos	0.007	0.015	0.667

Exhibit 9.2.4.6c. Stanford Binet: Copying
Plot of Predicted Values of Y



Notes: Plot symbol indicates predicted value of Y when the values if *PreNatThimer* and *Exp07mos* are equal to the values shown below the x-axis. For example, the left-most plotting symbol shows the predicted value of Y when *PreNatThimer* = 0 and *Exp07mos* = 0. The next symbol to the right shows the predicted value when *PreNatThimer* = 0 and *Exp07mos* = 11.6, and so on.

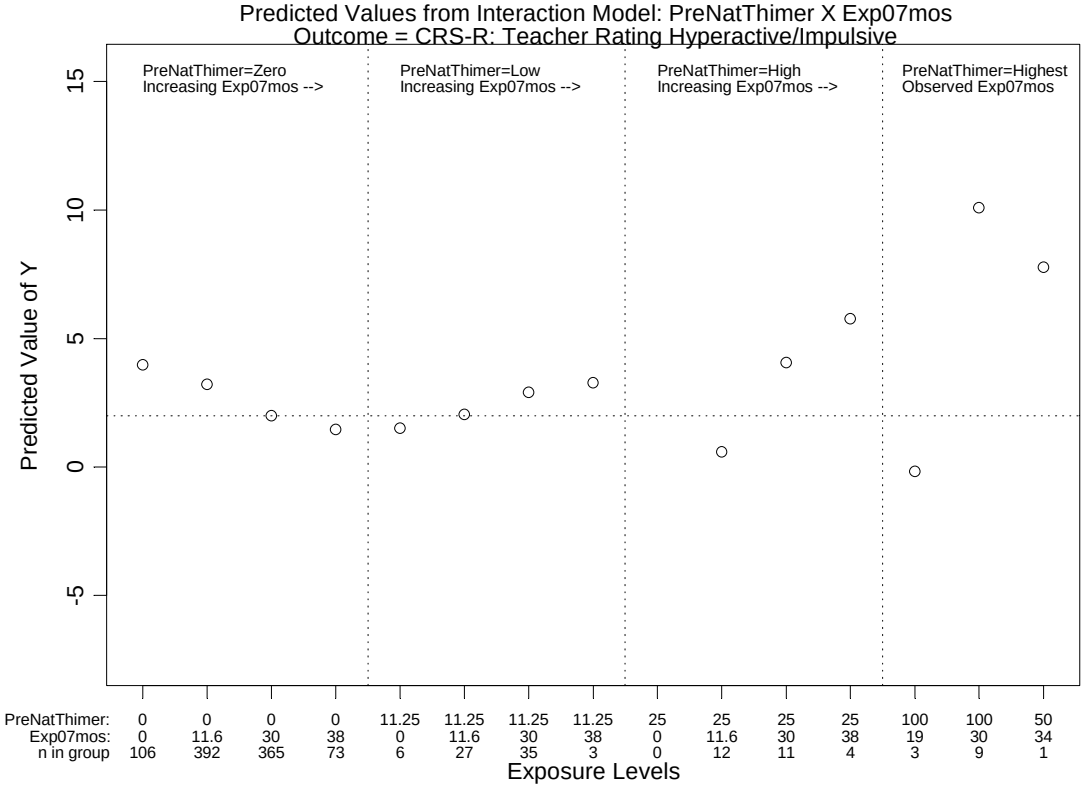
Exhibit 9.2.4.7a. CRS-R: Teacher--Hyperactive/Impulsive Cluster
Summary of Regression Coefficients from Interaction Model

Variable Name	Estimate	Standard Error	P-Value
PreNatThimer	-0.219	0.090	0.015
Exp07mos	-0.066	0.034	0.054
PreNatThimer*Exp07mos	0.010	0.004	0.006

Exhibit 9.2.4.7b. CRS-R: Teacher--Hyperactive/Impulsive Cluster
Summary of Regression Coefficients from Model Without The Interaction

Variable Name	Estimate	Standard Error	P-Value
PreNatThimer	0.023	0.022	0.301
Exp07mos	-0.048	0.034	0.157

Exhibit 9.2.4.7c. CRS-R: Teacher--Hyperactive/Impulsive Cluster
Plot of Predicted Values of Y



Notes: Plot symbol indicates predicted value of Y when the values if *PreNatThimer* and *Exp07mos* are equal to the values shown below the x-axis. For example, the left-most plotting symbol shows the predicted value of Y when *PreNatThimer* = 0 and *Exp07mos* = 0. The next symbol to the right shows the predicted value when *PreNatThimer* = 0 and *Exp07mos* = 11.6, and so on.

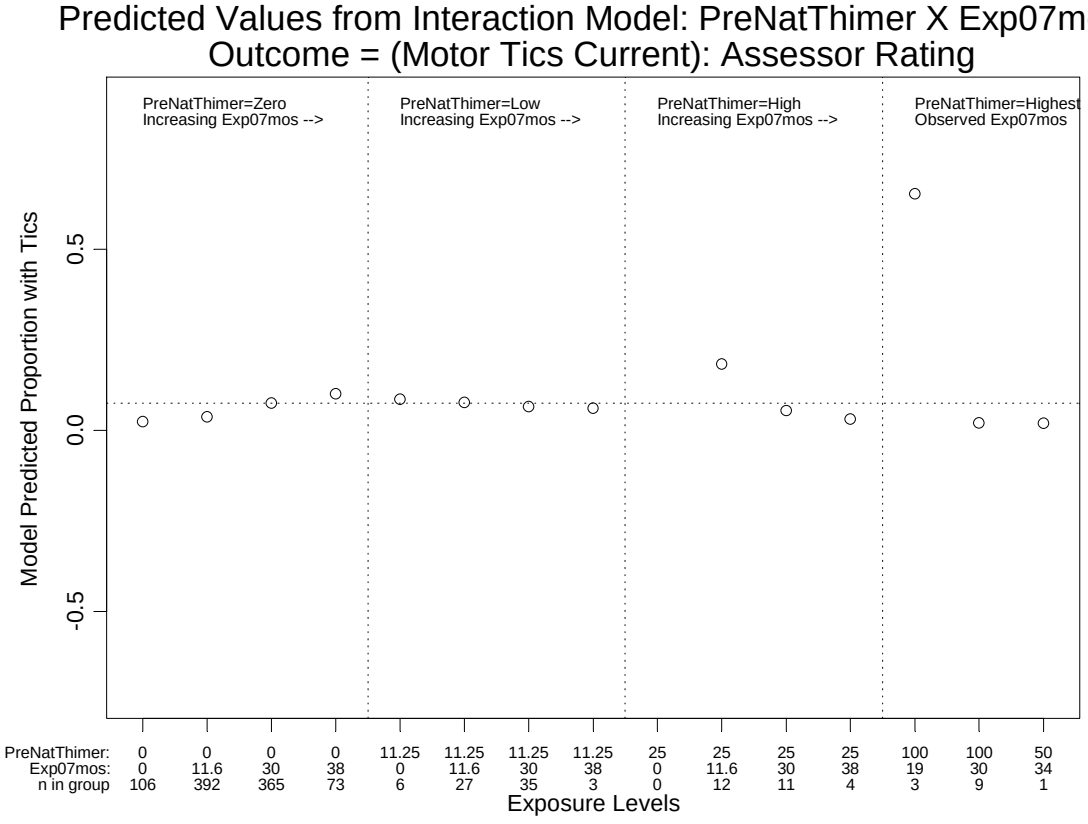
Exhibit 9.2.4.9a. Assessor Rated Motor Tics
Summary of Regression Coefficients from Interaction Model

Variable Name	Estimate	Standard Error	P-Value
PreNatThimer	0.121	0.051	0.017
Exp07mos	0.040	0.022	0.070
PreNatThimer*Exp07mos	-0.004	0.002	0.046

Exhibit 9.2.4.9b. Assessor Rated Motor Tics
Summary of Regression Coefficients from Model Without The Interaction

Variable Name	Estimate	Standard Error	P-Value
PreNatThimer	0.017	0.011	0.104
Exp07mos	0.032	0.022	0.142

Exhibit 9.2.4.9c. Assessor Rated Motor Tics
Plot of Predicted Values of Y



Notes: Plot symbol indicates predicted value of Y when the values if *PreNatThimer* and *Exp07mos* are equal to the values shown below the x-axis. For example, the left-most plotting symbol shows the predicted value of Y when *PreNatThimer* = 0 and *Exp07mos* = 0. The next symbol to the right shows the predicted value when *PreNatThimer* = 0 and *Exp07mos* = 11.6, and so on.

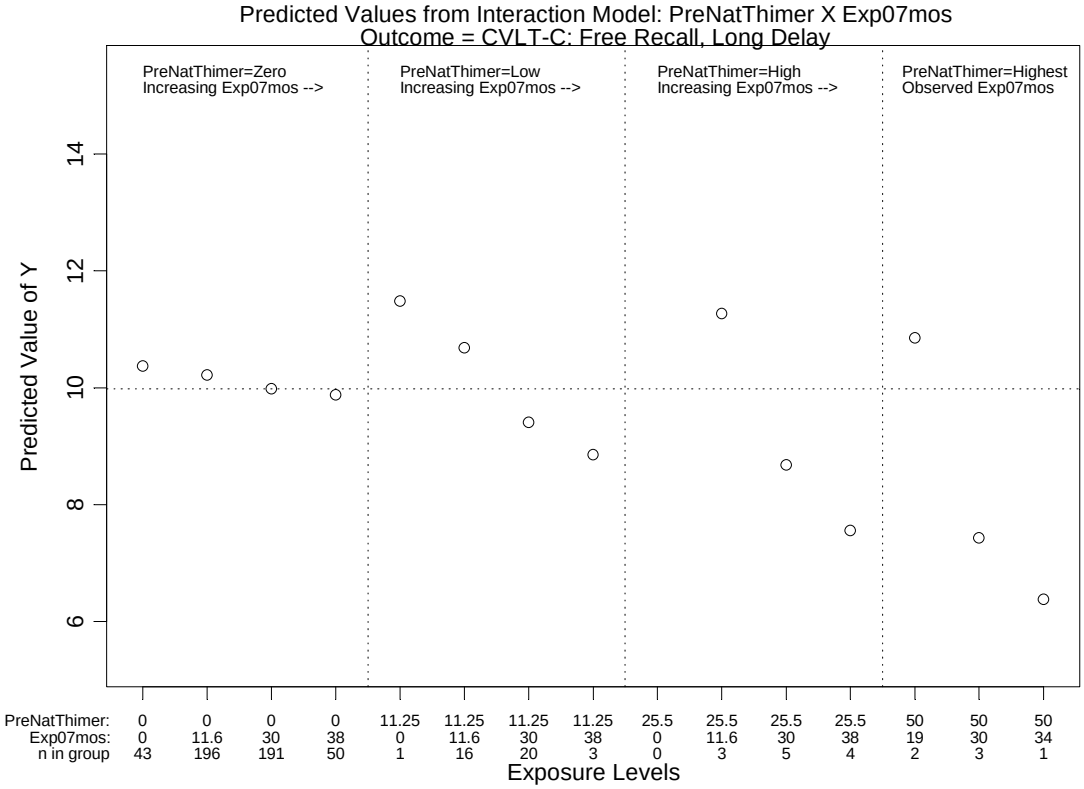
Exhibit 9.2.4.9a. Females – CVLT-C: Free Recall Long Delay
Summary of Regression Coefficients from Interaction Model

Variable Name	Estimate	Standard Error	P-Value
PreNatThimer	0.099	0.050	0.047
Exp07mos	-0.013	0.017	0.435
PreNatThimer*Exp07mos	-0.005	0.002	0.023

Exhibit 9.2.4.9b. Females – CVLT-C: Free Recall Long Delay
Summary of Regression Coefficients from Model Without The Interaction

Variable Name	Estimate	Standard Error	P-Value
PreNatThimer	-0.010	0.013	0.446
Exp07mos	-0.022	0.017	0.190

Exhibit 9.2.4.9c. Females – CVLT-C: Free Recall Long Delay
Plot of Predicted Values of Y



Notes: Plot symbol indicates predicted value of Y when the values if *PreNatThimer* and *Exp07mos* are equal to the values shown below the x-axis. For example, the left-most plotting symbol shows the predicted value of Y when *PreNatThimer* = 0 and *Exp07mos* = 0. The next symbol to the right shows the predicted value when *PreNatThimer* = 0 and *Exp07mos* = 11.6, and so on.

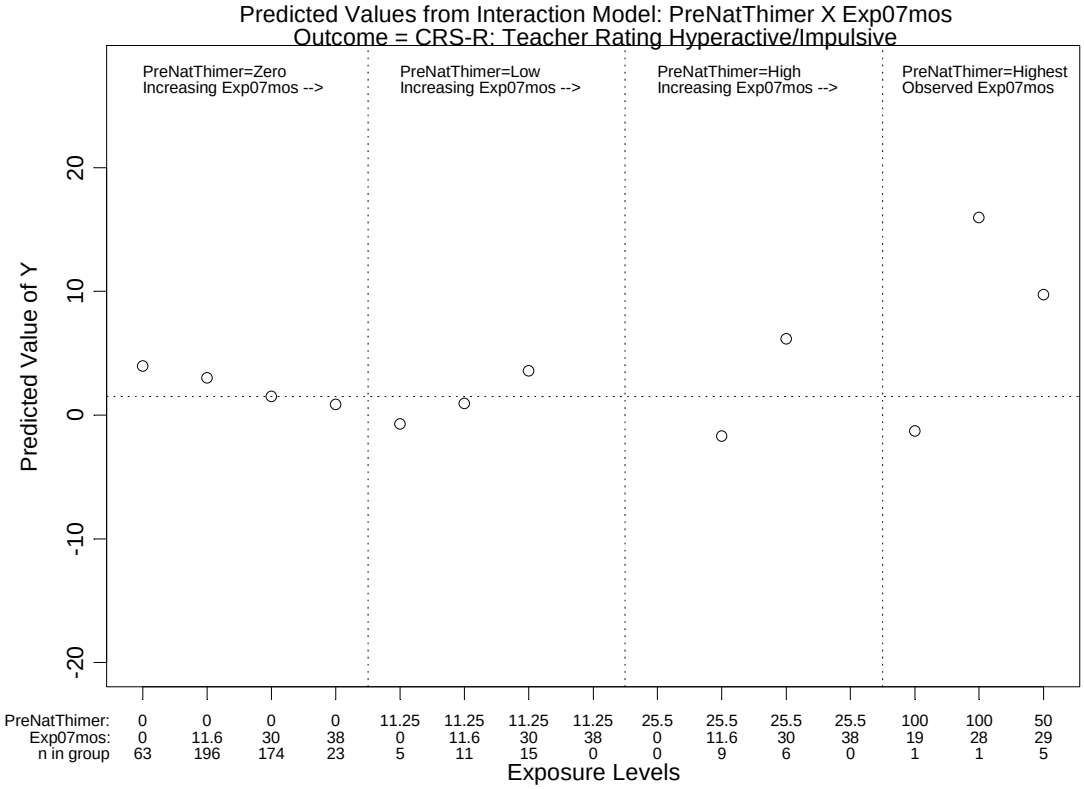
Exhibit 9.2.4.10a. Males – CRS-R: Teacher--Hyperactive/Impulsive Cluster
Summary of Regression Coefficients from Interaction Model

Variable Name	Estimate	Standard Error	P-Value
PreNatThimer	-0.417	0.147	0.005
Exp07mos	-0.082	0.056	0.144
PreNatThimer*Exp07mos	0.020	0.006	0.002

Exhibit 9.2.4.10b. Males – CRS-R: Teacher--Hyperactive/Impulsive Cluster
Summary of Regression Coefficients from Model Without The Interaction

Variable Name	Estimate	Standard Error	P-Value
PreNatThimer	0.036	0.034	0.291
Exp07mos	-0.058	0.056	0.303

Exhibit 9.2.4.10c. Males – CRS-R: Teacher--Hyperactive/Impulsive Cluster
Plot of Predicted Values of Y



Notes: Plot symbol indicates predicted value of Y when the values if *PreNatThimer* and *Exp07mos* are equal to the values shown below the x-axis. For example, the left-most plotting symbol shows the predicted value of Y when *PreNatThimer* = 0 and *Exp07mos* = 0. The next symbol to the right shows the predicted value when *PreNatThimer* = 0 and *Exp07mos* = 11.6, and so on.

9.2.5. Models for Multiple Sources of Prenatal Exposure Interacted with Postnatal Exposure from Thimerosal

9.2.5.1. Introduction

The models summarized in this section were motivated by the same hypothesis as described in the previous section – that is, children who had prenatal exposure to mercury could be more susceptible to additional doses of postnatal exposure than children who were not exposed in utero. In the current section, however, a broader measure of prenatal exposure is introduced and modeled. The broader measures of prenatal exposure includes mercury exposures from thimerosal in vaccines and immune globulins, maternal fish consumption, maternal use of mercury containing health care produces (contact lens, nasal, ear, eye drops), maternal exposure from home products, and from amalgam fillings. This new measure was modeled as an interaction effect with cumulative exposure from birth through seven months.

The broader measure of prenatal exposure was created by dichotomizing the component variables[17] into categories "1 = any exposure", and "0 = no exposure", and summing to create a composite score. The following variables were summed to create the composite (named *PrenatAllMerc*):

Variable			**Defintion**	
Pre_VacIG	{	= 0	if *PreNatThimer* = 0	}
		= 1	if *PreNatThimer* > 0	
Pre_Tuna	{	= 1	if *PreNatTuna* > 0	}
		= 0	if *PrenatTuna* = 0	
PreOrg	{	= 0	*PreNatOrgMerc* = 0	}
		= 1	if *PreNatOrgMerc* > 0	
PreAmalgam	{	= 0	if *PreNatFillings* = 0	}
		= 1	if *PreNatFillings* > 0	
PreNatFish		=	*PreNatFish* variable as currently defined (0/1).	
PreNatHomePro		=	*PreNatHomePro* as currently defined (0/1).	
PreNatAllMerc		=	*Pre_VacIG* + *Pre_Tuna* + *PreOrg* + *PreAmalgam* + *PreNatFish* + P*reNatHomePro*	

A frequency crosstab of the *PreNatAllMerc* variable crossed with the components used in its creation is shown in Exhibit 9.2.5.1.

[17] For definitions of component variables, see Section 7.3.

Exhibit 9.2.5.1. PreNatAllMerc_1 Crossed with Six Component Variables Used to Construct It

PreNat AllMerc _1	PreNat Thimer	PreNat Tuna _1	PreNat Fish _1	PreNat OrgMerc _1	PreNat Home Pro_1	PreNat Fillings _1	Freq.	Percent	Cum. Freq.	Cum. Percent
0	0	0	0	0	0	0	71	6.78	71	6.78
1	0	0	0	0	0	1	36	3.44	107	10.22
1	0	0	0	0	0	2	170	16.24	277	26.46
1	0	0	0	0	1	0	1	0.1	278	26.55
1	0	0	0	2	0	0	1	0.1	279	26.65
1	0	1	0	0	0	0	87	8.31	366	34.96
1	0	2	0	0	0	0	6	0.57	372	35.53
1	12.75	0	0	0	0	0	3	0.29	375	35.82
1	25	0	0	0	0	0	1	0.1	376	35.91
2	0	0	0	0	1	1	1	0.1	377	36.01
2	0	0	0	0	1	2	3	0.29	380	36.29
2	0	0	0	1	0	1	1	0.1	381	36.39
2	0	0	0	1	0	2	1	0.1	382	36.49
2	0	0	0	2	0	1	2	0.19	384	36.68
2	0	0	0	2	0	2	10	0.96	394	37.63
2	0	1	0	0	0	1	53	5.06	447	42.69
2	0	1	0	0	0	2	354	33.81	801	76.5
2	0	1	0	0	1	0	1	0.1	802	76.6
2	0	1	0	1	0	0	1	0.1	803	76.7
2	0	1	0	2	0	0	4	0.38	807	77.08
2	0	1	0	3	0	0	1	0.1	808	77.17
2	0	1	1	0	0	0	8	0.76	816	77.94
2	0	2	0	0	0	1	3	0.29	819	78.22
2	0	2	0	0	0	2	19	1.81	838	80.04
2	11.25	0	0	0	0	1	1	0.1	839	80.13
2	12.75	0	0	0	0	1	2	0.19	841	80.32
2	12.75	0	0	0	0	2	12	1.15	853	81.47
2	12.75	1	0	0	0	0	3	0.29	856	81.76
2	12.75	2	0	0	0	0	1	0.1	857	81.85
2	25	0	0	0	0	2	2	0.19	859	82.04
2	25	1	0	0	0	0	2	0.19	861	82.23
2	25.5	0	0	0	0	2	1	0.1	862	82.33
2	50	0	0	0	0	2	3	0.29	865	82.62
2	50	1	0	0	0	0	1	0.1	866	82.71
2	100	0	0	0	0	2	1	0.1	867	82.81
3	0	0	0	2	1	2	1	0.1	868	82.9
3	0	1	0	0	1	1	2	0.19	870	83.09
3	0	1	0	0	1	2	19	1.81	889	84.91
3	0	1	0	1	0	2	8	0.76	897	85.67
3	0	1	0	2	0	1	3	0.29	900	85.96
3	0	1	0	2	0	2	15	1.43	915	87.39
3	0	1	1	0	0	1	2	0.19	917	87.58
3	0	1	1	0	0	2	34	3.25	951	90.83
3	0	2	0	0	1	1	1	0.1	952	90.93
3	0	2	0	0	1	2	1	0.1	953	91.02
3	0	2	0	2	0	2	2	0.19	955	91.21
3	0	2	1	0	0	2	4	0.38	959	91.6
3	12.5	1	0	0	0	2	1	0.1	960	91.69
3	12.75	0	0	0	1	2	1	0.1	961	91.79
3	12.75	0	0	2	0	2	1	0.1	962	91.88
3	12.75	1	0	0	0	1	3	0.29	965	92.17

Exhibit 9.2.5.1. PreNatAllMerc_1 Crossed with Six Component Variables Used to Construct It

PreNat AllMerc _1	PreNat Thimer	PreNat Tuna _1	PreNat Fish _1	PreNat OrgMerc _1	PreNat Home Pro_1	PreNat Fillings _1	Freq.	Percent	Cum. Freq.	Cum. Percent
3	12.75	1	0	0	0	2	29	2.77	994	94.94
3	12.75	1	1	0	0	0	2	0.19	996	95.13
3	12.75	2	0	0	0	2	1	0.1	997	95.22
3	25	1	0	0	0	1	1	0.1	998	95.32
3	25	1	0	0	0	2	7	0.67	1005	95.99
3	25	1	1	0	0	0	1	0.1	1006	96.08
3	25	2	0	0	0	2	2	0.19	1008	96.28
3	25.5	1	0	0	0	1	1	0.1	1009	96.37
3	25.5	1	0	0	0	2	5	0.48	1014	96.85
3	25.5	2	0	0	0	2	1	0.1	1015	96.94
3	50	0	0	0	1	2	1	0.1	1016	97.04
3	50	0	0	2	0	2	1	0.1	1017	97.13
3	50	1	0	0	0	2	2	0.19	1019	97.33
3	62.75	2	0	0	0	2	1	0.1	1020	97.42
3	100	1	0	0	0	2	1	0.1	1021	97.52
4	0	1	0	1	1	2	1	0.1	1022	97.61
4	0	1	1	0	1	2	4	0.38	1026	97.99
4	0	1	1	1	0	1	1	0.1	1027	98.09
4	0	1	1	2	0	2	2	0.19	1029	98.28
4	0	1	1	4	0	2	1	0.1	1030	98.38
4	12.75	1	0	2	0	2	5	0.48	1035	98.85
4	12.75	1	1	0	0	2	6	0.57	1041	99.43
4	25	1	1	0	0	2	2	0.19	1043	99.62
4	25.5	2	1	0	0	2	1	0.1	1044	99.71
4	50	1	0	0	1	2	1	0.1	1045	99.81
4	50	1	0	2	0	2	1	0.1	1046	99.9
5	0	1	1	2	1	2	1	0.1	1047	100

9.2.5.2. Model Specifications

Interaction Model

This model tests for an interaction effect of *PreNatAllMerc* and *Exp07mos*.

$$Y = \beta_0 + \beta_1 preNatAllMerc + \beta_2 Exp07mos + \beta_3 preNatAllMerc * Exp07mos + \sum_j \alpha_j oe_j + \sum_k \alpha_{j+k} cf_k + \sum_l \alpha_{j+k+l} St_l + \varepsilon$$

$$H_0 : \beta_3 = 0 \quad vs \quad H_a : \beta_3 \neq 0$$

Main Effect Model

The summary table also shows results from models where the non-significant interaction effects were dropped. These models are of the form:

$$Y = \beta_0 + \beta_1 preNatAllMerc + \beta_2 Exp07mos + \sum_j \alpha_j oe_j + \sum_k \alpha_{j+k} cf_k + \sum_l \alpha_{j+k+l} St_l + \varepsilon$$

$$H_0 : \beta_1 = 0 \quad vs \quad H_a : \beta_1 \neq 0$$

9.2.5.3. Results

Results are summarized in Exhibit 9.2.5.2. There were two significant *PreNatAllMerc* by *Exp07mos* interaction effects. Similar to the results in the previous section, both sets of significant results were cases where the signs of the coefficients for prenatal, postnatal, and interaction effects were not consistent. For these two results, the coefficients for prenatal and postnatal effects were positive, while the coefficient for the interaction effect was negative. And, comparing the coefficient from the interaction model in the right-hand panel of the summary, to the main effect model in the left-hand panel of the summary, it is evident that the addition of the interaction term substantially increased the size of the estimated positive coefficients for both main effects, with offsetting negative interaction effects.

The exhibit also highlights three interaction effects that fell below a $p<0.10$ criterion. In none of these three cases were the coefficients for the prenatal, postnatal, and interaction effects in a consistent direction of either benefit or harm.

Similar to the results from the previous section, none of the interaction effects shown in Exhibit 9.2.5.2 suggest clear evidence of either harm or benefit associated with the interaction between prenatal and postnatal exposure.

Exhibit 9.2.5.2. Summary of Multiple Sources of Prenatal Mercury Models (n=1,047)

	Main Effects Model						Interaction Model								
	PreNatAllMerc			Exp07mos			PreNatAllMerc			Exp07mos			PreNatAllMerc X Exp07 mos		
Test	Est	S.E.	P	Est	S.E.	P	Est	S.E.	P	Est	S.E.	P	Est	S.E.	P
Speech and Language															
Boston Naming Test	0.430	0.276	0.119	0.051	0.030	0.090	1.103	0.655	0.093	0.113	0.063	0.071	-0.034	0.030	0.258
NEPSY: Speeded Naming	1.675	0.588	0.004+	0.012	0.038	0.753	1.392	0.963	0.149	-0.014	0.079	0.863	0.014	0.038	0.711
NEPSY: Comprehension of Instructions	0.211	0.210	0.315	-0.014	0.014	0.301	0.344	0.343	0.317	-0.002	0.028	0.947	-0.007	0.014	0.625
CELF: Formulated Sentences	-0.060	0.207	0.772	-0.034	0.030	0.248	0.691	0.612	0.259	0.036	0.062	0.560	-0.038	0.029	0.193
CELF: Recalling Sentences	0.244	0.482	0.612	0.001	0.062	0.982	1.008	1.290	0.435	0.073	0.128	0.569	-0.039	0.061	0.524
GFTA: Articulation (lower = better)	-0.034	0.067	0.611	0.011	0.010	0.254	-0.173	0.197	0.381	-0.002	0.020	0.919	0.007	0.009	0.455
Stuttering: Assessor Rating (lower = better)	-0.116	0.208	0.579	0.025	0.033	0.438	0.402	0.633	0.525	0.071	0.062	0.254	-0.026	0.030	0.387
Stuttering: Parent Rating (lower = better)	-0.188	0.265	0.478	0.020	0.043	0.631	-1.263	0.887	0.154	-0.069	0.082	0.397	0.058	0.045	0.199
Stuttering: Teacher Rating (lower = better)	-0.132	0.180	0.465	0.008	0.025	0.754	0.575	0.552	0.297	0.068	0.051	0.183	-0.036	0.027	0.177
Verbal Memory															
CVLT-C: Free Recall, No Delay	0.364	0.476	0.444	-0.001	0.046	0.991	0.584	1.019	0.567	0.020	0.097	0.835	-0.011	0.046	0.807
CVLT-C: Free Recall, Short Delay	0.183	0.115	0.113	-0.024	0.013	0.070	0.219	0.282	0.438	-0.020	0.027	0.455	-0.002	0.013	0.887
CVLT-C: Cued Recall, Short Delay	0.029	0.084	0.734	-0.005	0.011	0.637	0.009	0.237	0.970	-0.007	0.024	0.760	0.001	0.011	0.929
CVLT-C: Free Recall, Long Delay	0.102	0.122	0.401	-0.019	0.012	0.111	0.294	0.265	0.268	-0.001	0.025	0.957	-0.010	0.012	0.416
CVLT-C: Cued Recall, Long Delay	0.211	0.183	0.249	0.001	0.012	0.924	0.210	0.300	0.484	0.001	0.025	0.966	0.000	0.012	0.997
CMS Stories 1: Immediate Recall	0.353	0.416	0.396	-0.029	0.059	0.630	2.766	1.224	0.024+	0.198	0.123	0.109	-0.123	0.059	0.036*
CMS Stories 2: Delayed Recall	0.401	0.476	0.400	0.004	0.059	0.948	2.823	1.216	0.020+	0.234	0.121	0.054	-0.125	0.058	0.031*
Achievement															
WJIII: Letter- Word Identification	-0.350	0.300	0.243	0.063	0.037	0.090	0.819	0.764	0.284	0.173	0.076	0.023+	-0.060	0.036	0.097
Fine Motor Coordination															
Grooved Pegboard: Dominant Hand (lower = better)	-0.688	0.737	0.351	-0.085	0.089	0.339	0.418	1.880	0.824	0.019	0.185	0.920	-0.057	0.089	0.523
Grooved Pegboard: Non-dom Hand (lower = better)	-1.191	1.393	0.393	-0.278	0.109	0.011+	-0.165	2.594	0.949	-0.185	0.227	0.415	-0.051	0.109	0.639
Finger Tapping: Dominant Hand	-0.186	0.216	0.389	0.033	0.031	0.288	-0.046	0.639	0.942	0.046	0.064	0.473	-0.007	0.031	0.815
Finger Tapping: Non-dominant Hand	-0.136	0.269	0.612	0.017	0.028	0.539	0.191	0.613	0.755	0.048	0.058	0.414	-0.017	0.028	0.552
Visual Spatial Ability															
Stanford Binet: Copying	0.093	0.185	0.613	0.007	0.015	0.655	0.287	0.358	0.424	0.024	0.032	0.443	-0.009	0.015	0.529
Attention/Executive Functioning															
GDS Vigilance Task: Correct Responses	0.049	0.328	0.881	0.032	0.026	0.220	-0.443	0.610	0.467	-0.014	0.054	0.799	0.025	0.026	0.338
GDS Vigilance Task: Errors (lower = better)	0.275	0.624	0.660	-0.020	0.067	0.766	0.927	1.440	0.520	0.041	0.139	0.766	-0.033	0.066	0.615
WISC III: Digit Span, Forward Recall	-0.057	0.077	0.462	-0.002	0.010	0.819	0.277	0.199	0.164	0.029	0.020	0.138	-0.017	0.009	0.069
WISC III: Digit Span, Backward Recall	-0.027	0.058	0.647	0.017	0.008	0.035+	0.113	0.171	0.508	0.030	0.017	0.075	-0.007	0.008	0.384
WISC III: Digit Span, Combined	-0.083	0.113	0.463	0.016	0.015	0.259	0.394	0.303	0.193	0.061	0.030	0.042+	-0.024	0.014	0.090
BRIEF Parent Rating: Metacognition (lower = better)	-0.890	0.927	0.338	-0.052	0.092	0.573	-1.950	2.024	0.336	-0.151	0.191	0.431	0.054	0.092	0.556
BRIEF Teacher Rating: Metacognition (lower = better)	-1.105	1.631	0.498	-0.145	0.132	0.275	-1.300	3.158	0.681	-0.162	0.274	0.554	0.009	0.131	0.943
Behavior Regulation (lower = better)															
CRS-R: Parent Rating: Hyperactive/Impulsive	-0.078	0.191	0.684	0.019	0.026	0.464	-0.348	0.539	0.519	-0.006	0.053	0.909	0.014	0.026	0.592
CRS-R: Teacher Rating: Hyperactive/Impulsive	0.241	0.313	0.442	-0.046	0.034	0.171	-0.580	0.740	0.433	-0.121	0.069	0.083	0.041	0.033	0.221
CRS-R: Parent Rating: Inattentive	-0.122	0.295	0.678	-0.023	0.030	0.439	-0.411	0.665	0.537	-0.050	0.063	0.427	0.015	0.030	0.629
CRS-R: Teacher Rating: Inattentive	-0.127	0.481	0.791	-0.034	0.043	0.433	-0.212	1.012	0.834	-0.041	0.089	0.642	0.004	0.043	0.924
BRIEF Parent Rating: Behavior Regulation	-0.974	0.518	0.060	0.073	0.055	0.184	-1.679	1.208	0.165	0.009	0.114	0.939	0.035	0.055	0.518
BRIEF Teacher Rating: Behavior Regulation	-0.014	0.526	0.978	-0.042	0.072	0.557	-0.196	1.491	0.896	-0.059	0.148	0.689	0.009	0.070	0.897
Tics (lower = better)															
Motor tics (current): Assessor Rating	0.086	0.197	0.662	0.033	0.022	0.133	0.376	0.489	0.441	0.058	0.045	0.194	-0.014	0.021	0.516
Phonics tics (current): Assessor Rating	0.189	0.213	0.375	0.038	0.023	0.095	0.188	0.540	0.727	0.038	0.049	0.431	0.000	0.025	0.999
Motor tics (current): Parent Rating	0.087	0.219	0.693	-0.001	0.021	0.971	0.235	0.447	0.600	0.013	0.042	0.753	-0.008	0.020	0.703
Phonics tics (current): Parent Rating	0.140	0.163	0.391	0.007	0.019	0.693	0.359	0.390	0.357	0.028	0.038	0.465	-0.011	0.018	0.537
General Intellectual Functioning															
WASI Verbal IQ	0.366	0.513	0.475	-0.040	0.066	0.538	1.696	1.378	0.219	0.084	0.136	0.539	-0.068	0.065	0.299
WASI Performance IQ	0.903	0.583	0.122	0.130	0.074	0.080	0.634	1.558	0.684	0.105	0.154	0.496	0.014	0.074	0.852
WASI Full Scale IQ	0.721	0.523	0.168	0.061	0.068	0.370	1.616	1.401	0.249	0.145	0.140	0.300	-0.046	0.067	0.491

Key: Mercury effect = Better Outcome — < .05: p-value+; >.05, <.10: p-value

Mercury effect =Worse Outcome — < .05: p-value*; >.05, <.10: p-value

P-values shown are rounded to 3 decimal places. Therefore, a value shown as 0.050 may satisify p<0.05 criterion if the original value was rounded up, or may not satisify the criterion if the value was rounded down.

9.2.6. Concurrent Antibiotics-by-Exposure Interaction Models

9.2.6.1. Introduction

Several studies of the rates of excretion of methylmercuric chloride in rodents have indicated that oral antibiotics taken concurrently with oral ingestion of methylmercuric chloride is associated with slower excretion (Rowland et. al., 1977, 1980,1984). The results of these studies suggest that antibiotics may interact with mercury in a way that may alter the effects of mercury. These finding motivate the hypothesis that, in children, antibiotics may interact with exposure to ethylmercury from thimerosal in vaccines, to have an effect that is different from exposure to ethylmercury from vaccines absent antibiotics use.

The models summarized in this section were fit to the data in order to explore the concurrent antibiotics hypothesis. Exposure to ethylmercury from thimerosal was defined as "concurrent with antibiotic receipt" if the thimerosal-containing vaccine was received during the course of antibiotic treatment, or was received up to 14 days prior to initiation of antibiotic treatment, or was received up to 14 days after the last day of antibiotic treatment. This definition of "concurrent with antibiotics" was the subject of much discussion and debate among the study's external consultants and principal investigators, and after consultation with the literature and several experts in toxicology, the current definition was considered to be the best available option. The rationale for this definition is as follows.

If we operate on the theory that the loss of normal flora by antibiotic treatment causes the thimerosal to be excreted more slowly from the body, we must include a period of time after antibiotic usage stops during which the normal flora returns to normal. Pediatric experts advised that E. coli (the most common gut bacteria) typically returns to normal levels within two weeks of antibiotic use.

The rational for the window prior to antibiotic use is based on the notion that it takes time for the mercury to be excreted, and if antibiotic treatment starts after receipt of a thimerosal containing vaccine, the antibiotic could slow the excretion rate of the previously received, but unexcreted mercury. A consulting toxicologist advised that both animal and human data indicate demethylation and fecal excretion of the inorganic species is the predominant route of elimination of ethylmercury from the body. Unfortunately there are no precise numbers for the rate or biological half time of this process. Data from human infants (Pichichero et al, 2002), and infant monkeys (Burbacher et al., 2005) suggested that 14 days would be a reasonable guess at the length of one half-life for excretion.

9.2.6.2. Model Specifications

The following two models were fit to each outcome variable[18]:

Model (1): Concurrent Antibiotics from Birth to 7 Months

$$Y = \beta_0 + \beta_1 preNatThimer + \beta_2 Exp07mos + \beta_3 AbDays07mos + \beta_4 AbExp07mos + \sum_j \alpha_j oe_j + \sum_k \alpha_{j+k} cf_k + \sum_l \alpha_{j+k+l} St_l + \varepsilon$$

$$H_0 : \beta_4 = 0 \quad vs \quad H_a : \beta_4 \neq 0$$
$$H_0 : \beta_2 + \beta_4 = 0 \quad vs \quad H_a : \beta_2 + \beta_4 \neq 0$$

where

AbDays07mos = a count of the number of days that child received antibiotics, during the age range of 1 to 214 days,

and

AbExp07mos = a cumulative measure of ethylmercury exposure from thimerosal in vaccines received ***concurrent with antibiotics*** during the age range from birth through seven months (1 – 214 days), expressed in microgram units per kilograms of body weight at the time of vaccine receipt.

The parameter estimates have the following interpretations:

$\hat{\beta}_2$ is an estimate of the effect of exposure without concurrent antibiotic use.
$\hat{\beta}_3$ is an estimate of the effect of antibiotic use (note: not *concurrent* antibiotics, but antibiotics in and of themselves).
$\hat{\beta}_4$ is an estimate of the difference between exposure effects with concurrent antibiotic use and exposure effects without antibiotic use.
$\hat{\beta}_2 + \hat{\beta}_4$ is an estimate of the effect of exposure with concurrent antibiotic use (assuming the number of days on antibiotics is held constant).

Model (2): Concurrent Antibiotics from Birth to 1 Month, and 1 to 7 Months

$$Y = \beta_0 + \beta_1 preNatThimer + \beta_2 HepB + \beta_3 Exp17mos + \beta_4 AbDays01mos + \beta_5 AbDays17mos + \beta_6 AbExp01mos + \beta_7 AbExp17mos + \sum_j \alpha_j oe_j + \sum_k \alpha_{j+k} cf_k + \sum_l \alpha_{j+k+l} St_l + \varepsilon$$

[18] The models shown here are OLS regression models for continuous outcome variables. For dichotomous outcome measures (tics and stuttering) logistic regression models of a similar form were fit to the data.

$H_0 : \beta_6 = 0 \quad vs \quad H_a : \beta_6 \neq 0$

$H_0 : \beta_7 = 0 \quad vs \quad H_a : \beta_7 \neq 0$

$H_0 : \beta_2 + \beta_6 = 0 \quad vs \quad H_a : \beta_2 + \beta_6 \neq 0$

$H_0 : \beta_3 + \beta_7 = 0 \quad vs \quad H_a : \beta_3 + \beta_7 \neq 0$

where
AbDays01mos = a count of the number of days that child received antibiotics, during the first month of life (age range of 1 to 28 days),

AbDays17mos = a count of the number of days that child received antibiotics, during the during the age range of 1 to 7 months (age range of 29 to 214 days),
and

AbExp01mos = a cumulative measure of ethylmercury exposure from thimerosal in vaccines received ***concurrent with antibiotics*** during the age ranges from birth through one month1 (1 – 28 days), expressed in microgram units per kilograms of body weight at the time of vaccine receipt,

AbExp17mos = a cumulative measure of ethylmercury exposure from thimerosal in vaccines received ***concurrent with antibiotics*** during the age ranges from one through seven months (29 – 214 days), expressed in microgram units per kilograms of body weight at the time of vaccine receipt, and all other terms are as defined in the analysis plan.

The parameter estimates have the following interpretations:

$\hat{\beta}_2$ is an estimate of the effect of exposure without concurrent antibiotic use (during the age range spanning birth to 28 days).
$\hat{\beta}_3$ is an estimate of the effect of exposure without concurrent antibiotic use (during the age range spanning 29 days to seven months).
$\hat{\beta}_4$ is an estimate of the effect of antibiotic use during the age range spanning birth to 28 days. (note: not *concurrent* antibiotics, but antibiotics in and of themselves).
$\hat{\beta}_5$ is an estimate of the effect of antibiotic use during the age range spanning 29 days to seven months. (note: not *concurrent* antibiotics, but antibiotics in and of themselves).
$\hat{\beta}_6$ is an estimate of the difference between exposure effects with concurrent antibiotic use and exposure effects without antibiotic use, for the age range spanning birth to 28 days.
$\hat{\beta}_6$ is an estimate of the difference between exposure effects with concurrent antibiotic use and exposure effects without antibiotic use, for the age range spanning 29 days to seven months.
$\hat{\beta}_2 + \hat{\beta}_6$ is an estimate of the effect of exposure with concurrent antibiotic use, for the age range spanning birth to 28 days (assuming the number of days on antibiotics is held constant).

$\hat{\beta}_3 + \hat{\beta}_7$ is an estimate of the effect of exposure with concurrent antibiotic use, for the age range spanning 29 days to seven months.

9.2.6.3. Results

The results offer little support for the hypothesis that mercury from vaccines is more harmful if received concurrent with antibiotics. Of the 42 outcomes analyzed in the birth to seven months exposure model (Model 1), one, *CRS-R Teacher Rating Hyperactive / Impulsive*, had a significant exposure by antibiotics interaction effect[19]. For this outcome the model estimated a statistically non-significant beneficial effect of cumulative exposure during the age range from birth to seven months, when the exposures were not concurrent with antibiotics[20]. For exposures that were concurrent with antibiotics, the model estimates a harmful effect that was not statistically significant, but was approximately similar in magnitude to the beneficial effect of non-concurrent exposure[21]. Furthermore, the estimated effects of the antibiotics themselves, were significant in the direction of benefit.

For the *Assessor Rated Motor Tics* outcome measure, the results indicate a significant effect of concurrent exposure during the age range from birth to seven months. Holding the number of days on antibiotics constant, the model predicts increasing risk of tics with increasing concurrent exposure. However, the coefficient for the effect of the number of days on antibiotics (*AbDays07mos*) is negative. This means that the model predicts that an increase in the number of days on antibiotics results in lower risk for this outcome. The predictions from this model are such that a combination of high levels concurrent exposure with a high number of days on antibiotics, produces a lower estimated risk than is estimated for a combination of low concurrent exposure and few days on antibiotics.

The Model 2 estimates regarding exposure during the age range from 1 to 7 months on the same outcome, *CRS-R Teacher Rating Hyperactive / Impulsive*, mirror the previously described results from Model 1 regarding exposure from birth to 7 months. (See columns labeled "Exp17mos", "AbExp17mos", and "Concur Exp17mos effect" in Exhibit 9.2.6.2). There was also a significant interaction effect (exposure 1 to 7 months by antibiotics) for the F*inger Tapping Non-Dominant Hand* outcome measures. For this outcome, estimates for non-concurrent exposure are in the direction of benefit, while estimates for concurrent exposure are in the direction of harm. However, for this same outcome, concurrent exposure in the earlier age range (birth to 28 days) is in the direction of benefit. For *Finger Tapping: Dominant Hand*, the interaction effect for birth to 28 days is significant, and the beneficial effect of concurrent exposure during the age range spanning birth to 28 days is statistically significant.

[19] See the column labeled "AbExp07mos" in Exhibit 9.2.6.1.
[20] See the column labeled "Exp07mos" in Exhibit 9.2.6.1.
[21] See the column labeled " Concur Exp07mos Effect" in Exhibit 9.2.6.1.

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Exhibit 9.2.6.1. Summary of Models for Concurrent Antibiotics Effect –Birth to Seven Months (n=1,047)

Test	PreNatThimer				Exp07mos				AbDays07mos				AbExp07mos				Concur Exp07mos Effect			
	Est	S.E.	P	StCf	Est	S.E.	P	StCf	Est	S.E.	P	StCf	Est	S.E.	P	StCf	Est	S.E.	P	StCf
Speech and Language																				
Boston Naming Test	0.032	0.022	0.143	0.033	0.049	0.031	0.111	0.044	-0.008	0.014	0.544		0.006	0.058	0.911		0.056	0.060	0.352	0.050
NEPSY: Speeded Naming	0.058	0.027	0.031 +	0.060	0.017	0.039	0.670	0.015	-0.001	0.017	0.969		-0.066	0.073	0.368		-0.049	0.076	0.518	-0.043
NEPSY: Comprehension of Instructions	-0.002	0.010	0.867	-0.005	-0.013	0.014	0.356	-0.032	0.004	0.006	0.517		-0.008	0.026	0.759		-0.021	0.027	0.440	-0.053
CELF: Formulated Sentences	0.020	0.021	0.341	0.025	-0.035	0.030	0.247	-0.037	0.016	0.013	0.231		0.008	0.056	0.893		-0.028	0.059	0.637	-0.029
CELF: Recalling Sentences	0.057	0.044	0.201	0.033	-0.012	0.063	0.846	-0.006	-0.014	0.028	0.616		0.102	0.118	0.389		0.090	0.122	0.464	0.045
GFTA: Articulation (lower = better)	-0.002	0.007	0.800	-0.008	0.010	0.010	0.284	0.040	-0.004	0.004	0.313		0.003	0.018	0.859		0.014	0.019	0.469	0.052
Stuttering: Assessor Rating (lower = better)	-0.002	0.021	0.941	0.974	0.031	0.033	0.355	1.556	0.015	0.011	0.170		-0.048	0.062	0.437		-0.017	0.065	0.788	0.779
Stuttering: Parent Rating (lower = better)	-0.022	0.049	0.651	0.694	0.034	0.045	0.452	1.620	0.001	0.026	0.974		-0.188	0.114	0.100		-0.154	0.114	0.174	0.110
Stuttering: Teacher Rating (lower = better)	-0.039	0.029	0.176	0.519	0.009	0.026	0.721	1.140	0.010	0.008	0.187		-0.002	0.041	0.959		0.007	0.044	0.874	1.106
Verbal Memory																				
CVLT-C: Free Recall, No Delay	0.030	0.033	0.356	0.026	0.010	0.047	0.826	0.008	0.022	0.021	0.299		-0.112	0.088	0.205		-0.101	0.091	0.268	-0.074
CVLT-C: Free Recall, Short Delay	-0.001	0.009	0.895	-0.004	-0.023	0.013	0.085	-0.060	0.006	0.006	0.350		-0.007	0.025	0.795		-0.029	0.026	0.256	-0.077
CVLT-C: Cued Recall, Short Delay	-0.001	0.008	0.916	-0.003	-0.005	0.012	0.672	-0.015	0.001	0.005	0.919		-0.004	0.022	0.864		-0.009	0.023	0.701	-0.026
CVLT-C: Free Recall, Long Delay	0.001	0.009	0.926	0.003	-0.020	0.012	0.111	-0.055	0.001	0.006	0.837		0.003	0.023	0.880		-0.016	0.024	0.502	-0.045
CVLT-C: Cued Recall, Long Delay	0.005	0.008	0.563	0.016	0.002	0.012	0.900	0.004	0.001	0.005	0.904		-0.004	0.023	0.844		-0.003	0.024	0.901	-0.008
CMS Stories 1: Immediate Recall	0.025	0.042	0.555	0.013	-0.028	0.061	0.650	-0.013	-0.014	0.027	0.600		-0.032	0.113	0.781		-0.059	0.117	0.614	-0.027
CMS Stories 2: Delayed Recall	-0.009	0.041	0.826	-0.005	0.006	0.060	0.925	0.003	-0.010	0.027	0.711		-0.014	0.111	0.903		-0.008	0.116	0.946	-0.004
Achievement																				
WJIII: Letter- Word Identification	0.013	0.026	0.633	0.011	0.072	0.038	0.055	0.055	0.026	0.017	0.122		-0.094	0.070	0.182		-0.022	0.073	0.766	-0.017
Fine Motor Coordination																				
Grooved Pegboard: Dominant Hand (lower = better)	-0.111	0.064	0.084	-0.033	-0.081	0.091	0.370	-0.021	0.069	0.041	0.095		0.058	0.171	0.736		-0.024	0.177	0.894	-0.006
Grooved Pegboard: Non-dom Hand (lower = better)	-0.086	0.077	0.263	-0.023	-0.281	0.111	0.012 +	-0.063	0.078	0.050	0.118		0.118	0.207	0.569		-0.163	0.215	0.449	-0.037
Finger Tapping: Dominant Hand	-0.013	0.022	0.561	-0.016	0.044	0.032	0.167	0.046	0.004	0.014	0.764		-0.096	0.059	0.105		-0.052	0.061	0.397	-0.054
Finger Tapping: Non-dominant Hand	-0.013	0.020	0.511	-0.017	0.029	0.029	0.315	0.033	0.011	0.013	0.393		-0.103	0.054	0.055		-0.074	0.055	0.181	-0.085
Visual Spatial Ability																				
Stanford Binet: Copying	0.006	0.011	0.595	0.016	0.009	0.016	0.545	0.022	-0.001	0.007	0.874		-0.029	0.029	0.307		-0.020	0.030	0.502	-0.048
Attention/Executive Functioning																				
GDS Vigilance Task: Correct Responses	-0.012	0.018	0.505	-0.020	0.039	0.026	0.138	0.054	0.010	0.012	0.392		-0.063	0.049	0.198		-0.024	0.051	0.638	-0.033
GDS Vigilance Task: Errors (lower = better)	0.035	0.047	0.461	0.022	-0.005	0.068	0.947	-0.002	0.070	0.030	0.020*		-0.152	0.126	0.227		-0.157	0.131	0.232	-0.084
WISC III: Digit Span, Forward Recall	0.000	0.007	0.968	0.001	-0.002	0.010	0.859	-0.007	-0.002	0.004	0.687		-0.006	0.018	0.755		-0.007	0.019	0.695	-0.028
WISC III: Digit Span, Backward Recall	-0.013	0.006	0.030 *	-0.065	0.019	0.008	0.022 +	0.084	0.001	0.004	0.710		-0.012	0.016	0.447		0.007	0.016	0.658	0.032
WISC III: Digit Span, Combined	-0.012	0.010	0.258	-0.033	0.019	0.015	0.205	0.046	0.000	0.007	0.951		-0.019	0.028	0.498		0.000	0.029	1.000	0.000
BRIEF Parent Rating: Metacognition (lower = better)	0.019	0.066	0.770	0.009	-0.066	0.094	0.479	-0.026	-0.028	0.042	0.506		0.134	0.176	0.449		0.067	0.182	0.713	0.026
BRIEF Teacher Rating: Metacognition (lower = better)	0.022	0.088	0.800	0.008	-0.174	0.135	0.198	-0.055	-0.033	0.057	0.564		0.275	0.244	0.260		0.102	0.257	0.692	0.032
Behavior Regulation (lower = better)																				
CRS-R: Parent Rating: Hyperactive/Impulsive	0.005	0.019	0.776	0.009	0.009	0.026	0.727	0.013	-0.026	0.012	0.028+		0.082	0.050	0.098		0.091	0.051	0.075	0.128
CRS-R: Teacher Rating: Hyperactive/Impulsive	0.021	0.022	0.349	0.030	-0.065	0.034	0.057	-0.080	-0.029	0.015	0.049+		0.177	0.062	0.005*		0.112	0.065	0.088	0.138
CRS-R: Parent Rating: Inattentive	0.011	0.022	0.609	0.015	-0.024	0.031	0.440	-0.029	0.001	0.014	0.934		0.002	0.058	0.967		-0.021	0.060	0.720	-0.026
CRS-R: Teacher Rating: Inattentive	0.001	0.029	0.967	0.001	-0.039	0.044	0.372	-0.038	-0.002	0.019	0.927		0.060	0.080	0.458		0.020	0.085	0.812	0.020
BRIEF Parent Rating: Behavior Regulation	-0.023	0.040	0.556	-0.018	0.060	0.057	0.287	0.040	-0.037	0.026	0.151		0.144	0.106	0.176		0.204	0.110	0.063	0.134
BRIEF Teacher Rating: Behavior Regulation	0.033	0.048	0.488	0.023	-0.061	0.073	0.402	-0.036	-0.019	0.031	0.529		0.174	0.132	0.187		0.113	0.139	0.417	0.067
Tics (lower = better)																				
Motor tics (current): Assessor Rating	0.017	0.011	0.119	1.320	0.025	0.022	0.265	1.429	-0.027	0.015	0.078		0.059	0.039	0.130		0.084	0.040	0.037*	3.310
Phonics tics (current): Assessor Rating	-0.011	0.018	0.538	0.829	0.034	0.023	0.151	1.618	-0.002	0.009	0.839		0.024	0.038	0.522		0.058	0.040	0.142	2.291
Motor tics (current): Parent Rating	0.003	0.012	0.834	1.043	-0.003	0.021	0.876	0.955	-0.013	0.010	0.185		-0.005	0.041	0.893		-0.009	0.042	0.834	0.883
Phonics tics (current): Parent Rating	-0.013	0.017	0.443	0.810	0.012	0.019	0.538	1.183	0.007	0.007	0.344		-0.041	0.036	0.260		-0.029	0.037	0.439	0.661
General Intellectual Functioning																				
WASI Verbal IQ	0.052	0.047	0.270	0.029	-0.055	0.067	0.414	-0.027	-0.014	0.030	0.651		0.104	0.126	0.409		0.049	0.130	0.705	0.024
WASI Performance IQ	-0.008	0.054	0.887	-0.004	0.130	0.076	0.086	0.061	-0.023	0.034	0.496		-0.016	0.144	0.910		0.114	0.149	0.445	0.053
WASI Full Scale IQ	0.026	0.048	0.595	0.015	0.057	0.069	0.412	0.028	-0.016	0.031	0.600		0.019	0.129	0.884		0.076	0.134	0.573	0.037

	< .05	>.05, <.10		< .05	>.05, <.10
Key: Mercury effect = Better Outcome	p-value+	p-value	Mercury effect =Worse Outcome	p-value*	p-value

P-values shown are rounded to 3 decimal places. Therefore, a value shown as 0.050 may satisfy p<0.05 criterion if the original value was rounded up, or may not satisfy the criterion if the value was rounded down.

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Exhibit 9.2.6.2. Summary of Models for Concurrent Antibiotics Effect –Birth to 28 Days, and 29 Days to Seven Months (n=1,047)

Test	PreNatThimer				HepB				Exp17mos				AbDays01mos				AbDays17mos				AbExp01mos				AbExp17mos				Concur HepB Effect				Concur Exp17mos Effect			
	Est	S.E.	P	StCf	Est	S.E.	P	StCf	Est	S.E.	P	StCf	Est	S.E.	P	StCf	Est	S.E.	P	StCf	Est	S.E.	P	StCf	Est	S.E.	P	StCf	Est	S.E.	P	StCf	Est	S.E.	P	StCf
Speech and Language																																				
Boston Naming Test	0.033	0.022	0.129	0.034	-0.047	0.102	0.643	-0.011	0.063	0.033	0.056	0.052	-0.173	0.109	0.112		0.001	0.015	0.942		0.101	0.342	0.767		-0.003	0.059	0.958		0.054	0.346	0.876	0.013	0.060	0.061	0.327	0.050
NEPSY: Speeded Naming	0.057	0.027	0.033+	0.059	-0.034	0.127	0.788	-0.008	0.024	0.042	0.573	0.019	-0.019	0.135	0.889		0.003	0.019	0.862		-0.801	0.424	0.059		-0.052	0.074	0.483		-0.835	0.429	0.052	-0.196	-0.028	0.077	0.713	-0.023
NEPSY: Comprehension of Instructions	-0.002	0.010	0.842	-0.006	-0.023	0.045	0.610	-0.016	-0.012	0.015	0.421	-0.028	0.028	0.049	0.566		0.003	0.007	0.681		-0.189	0.155	0.225		-0.003	0.027	0.918		-0.212	0.157	0.179	-0.143	-0.015	0.028	0.594	-0.035
CELF: Formulated Sentences	0.020	0.021	0.340	0.025	-0.064	0.099	0.518	-0.018	-0.030	0.032	0.356	-0.030	-0.089	0.106	0.399		0.023	0.015	0.116		-0.143	0.332	0.657		0.007	0.057	0.905		-0.207	0.336	0.538	-0.059	-0.023	0.060	0.698	-0.023
CELF: Recalling Sentences	0.054	0.044	0.224	0.031	-0.035	0.207	0.866	-0.005	-0.007	0.057	0.914	-0.003	-0.082	0.222	0.711		-0.005	0.031	0.877		-1.282	0.701	0.068		0.126	0.120	0.293		-1.317	0.708	0.063	-0.176	0.119	0.124	0.341	0.055
GFTA: Articulation (lower = better)	-0.002	0.007	0.715	-0.011	0.076	0.032	0.017*	0.077	0.003	0.010	0.794	0.010	0.008	0.034	0.821		-0.005	0.005	0.288		-0.040	0.108	0.715		0.006	0.019	0.755		0.036	0.109	0.740	0.037	0.008	0.019	0.669	0.030
Stuttering: Assessor Rating (lower = better)	-0.002	0.021	0.925	0.957	0.067	0.104	0.523	1.290	0.024	0.036	0.495	1.381	0.066	0.081	0.416		0.011	0.013	0.404		-0.068	0.295	0.818		-0.048	0.064	0.455		-0.001	0.299	0.997	0.996	-0.024	0.057	0.724	0.729
Stuttering: Parent Rating (lower = better)	-0.021	0.048	0.663	0.705	-0.095	0.125	0.447	0.696	0.046	0.046	0.324	1.840	-6.373	50.547	0.900		0.002	0.027	0.950		-0.839	69.395	0.990		-0.173	0.115	0.131		-0.934	69.395	0.989	0.028	-0.127	0.115	0.267	0.184
Stuttering: Teacher Rating (lower = better)	-0.038	0.029	0.183	0.529	0.030	0.075	0.689	1.122	0.010	0.028	0.726	1.137	-0.044	0.074	0.554		0.015	0.010	0.118		0.013	0.234	0.957		-0.006	0.041	0.878		0.043	0.237	0.857	1.178	0.003	0.045	0.940	1.046
Verbal Memory																																				
CVLT-C: Free Recall, No Delay	0.031	0.033	0.356	0.026	0.020	0.154	0.897	0.004	0.011	0.050	0.833	0.007	-0.065	0.165	0.694		0.027	0.023	0.238		-0.080	0.522	0.879		-0.115	0.089	0.198		-0.060	0.529	0.910	-0.012	-0.105	0.093	0.263	-0.072
CVLT-C: Free Recall, Short Delay	-0.001	0.009	0.896	-0.004	-0.017	0.044	0.695	-0.012	-0.023	0.014	0.103	-0.056	-0.024	0.047	0.617		0.007	0.007	0.260		-0.004	0.148	0.980		-0.008	0.025	0.768		-0.021	0.150	0.889	-0.015	-0.031	0.026	0.247	-0.075
CVLT-C: Cued Recall, Short Delay	-0.001	0.008	0.870	-0.005	0.030	0.038	0.432	0.024	-0.009	0.012	0.488	-0.024	-0.021	0.041	0.602		0.002	0.006	0.691		-0.107	0.131	0.415		-0.002	0.022	0.926		-0.077	0.132	0.561	-0.061	-0.011	0.023	0.643	-0.030
CVLT-C: Free Recall, Long Delay	0.001	0.009	0.943	0.002	-0.020	0.041	0.618	-0.015	-0.019	0.013	0.144	-0.050	-0.020	0.043	0.645		0.003	0.006	0.655		-0.057	0.137	0.627		0.004	0.024	0.863		-0.087	0.139	0.532	-0.065	-0.015	0.024	0.538	-0.040
CVLT-C: Cued Recall, Long Delay	0.005	0.008	0.565	0.016	0.008	0.040	0.835	0.006	0.001	0.013	0.918	0.004	-0.036	0.042	0.396		0.003	0.006	0.622		-0.003	0.135	0.984		-0.006	0.023	0.802		0.006	0.137	0.968	0.004	-0.004	0.024	0.854	-0.012
CMS Stories 1: Immediate Recall	0.024	0.042	0.572	0.013	-0.068	0.198	0.731	-0.008	-0.023	0.065	0.721	-0.010	0.029	0.212	0.891		-0.015	0.029	0.619		-0.642	0.667	0.336		-0.018	0.115	0.877		-0.711	0.675	0.293	-0.087	-0.041	0.120	0.733	-0.018
CMS Stories 2: Delayed Recall	-0.011	0.041	0.791	-0.006	-0.037	0.195	0.847	-0.005	0.011	0.054	0.859	0.005	-0.002	0.209	0.994		-0.007	0.029	0.814		-0.980	0.654	0.134		0.006	0.113	0.956		-1.018	0.662	0.125	-0.128	0.018	0.118	0.881	0.008
Achievement																																				
WJIII: Letter- Word Identification	0.013	0.026	0.609	0.012	-0.072	0.123	0.559	-0.015	0.090	0.040	0.024+	0.064	-0.059	0.132	0.656		0.032	0.018	0.078		-0.356	0.415	0.392		-0.096	0.071	0.179		-0.428	0.420	0.309	-0.087	-0.006	0.074	0.940	-0.004
Fine Motor Coordination																																				
Grooved Pegboard: Dominant Hand (lower = better)	-0.108	0.064	0.092	-0.033	-0.278	0.301	0.355	-0.019	-0.061	0.096	0.527	-0.015	0.133	0.323	0.680		0.063	0.045	0.159		0.518	1.011	0.608		0.047	0.174	0.787		0.240	1.023	0.815	0.017	-0.014	0.181	0.938	-0.003
Grooved Pegboard: Non-dom Hand (lower = better)	-0.090	0.077	0.244	-0.024	-0.165	0.364	0.651	-0.010	-0.296	0.119	0.013+	-0.062	0.252	0.388	0.517		0.072	0.054	0.185		-1.117	1.224	0.362		0.152	0.211	0.471		-1.281	1.237	0.301	-0.077	-0.144	0.220	0.511	-0.030
Finger Tapping: Dominant Hand	-0.012	0.022	0.573	-0.015	0.197	0.104	0.057	0.055	0.028	0.034	0.404	0.028	-0.152	0.110	0.168		0.011	0.015	0.493		0.719	0.351	0.041+		-0.115	0.061	0.053		0.916	0.355	0.010+	0.257	-0.086	0.062	0.164	-0.084
Finger Tapping: Non-dominant Hand	-0.012	0.020	0.560	-0.015	0.025	0.094	0.791	0.008	0.032	0.031	0.303	0.034	-0.127	0.100	0.207		0.017	0.014	0.221		0.490	0.318	0.124		-0.120	0.054	0.027*		0.515	0.322	0.110	0.157	-0.089	0.056	0.116	-0.095
Visual Spatial Ability																																				
Stanford Binet: Copying	0.006	0.011	0.560	0.017	-0.025	0.051	0.621	-0.016	0.014	0.017	0.408	0.031	-0.021	0.054	0.693		0.000	0.008	0.980		0.063	0.171	0.713		-0.033	0.029	0.264		0.038	0.172	0.828	0.024	-0.019	0.030	0.534	-0.042
Attention/Executive Functioning																																				
GDS Vigilance Task: Correct Responses	-0.011	0.018	0.540	-0.018	-0.014	0.086	0.875	-0.005	0.045	0.028	0.110	0.058	0.018	0.092	0.846		0.009	0.013	0.493		0.146	0.289	0.614		-0.068	0.050	0.172		0.132	0.292	0.651	0.049	-0.023	0.052	0.658	-0.030
GDS Vigilance Task: Errors (lower = better)	0.033	0.047	0.489	0.020	0.051	0.221	0.817	0.007	-0.009	0.072	0.905	-0.004	-0.040	0.236	0.866		0.080	0.033	0.015*		-0.992	0.744	0.183		-0.138	0.127	0.278		-0.941	0.752	0.211	-0.135	-0.147	0.134	0.271	-0.074
WISC III: Digit Span, Forward Recall	0.000	0.007	0.953	0.002	-0.014	0.032	0.649	-0.015	0.001	0.010	0.934	0.003	-0.063	0.034	0.065		0.002	0.005	0.646		-0.066	0.107	0.539		-0.007	0.018	0.705		-0.080	0.108	0.459	-0.081	-0.006	0.019	0.750	-0.022
WISC III: Digit Span, Backward Recall	-0.013	0.006	0.028*	-0.066	0.038	0.028	0.168	0.045	0.018	0.009	0.049+	0.071	-0.021	0.030	0.478		0.003	0.004	0.509		-0.002	0.093	0.979		-0.013	0.016	0.431		0.036	0.095	0.704	0.042	0.005	0.017	0.769	0.020
WISC III: Digit Span, Combined	-0.012	0.010	0.255	-0.033	0.017	0.049	0.732	0.011	0.021	0.016	0.195	0.046	-0.086	0.052	0.099		0.005	0.007	0.493		-0.060	0.165	0.715		-0.021	0.028	0.449		-0.044	0.167	0.794	-0.028	-0.001	0.029	0.978	-0.002
BRIEF Parent Rating: Metacognition (lower = better)	0.019	0.066	0.778	0.008	0.004	0.309	0.990	0.000	-0.072	0.100	0.474	-0.026	-0.167	0.332	0.616		-0.019	0.046	0.675		0.033	1.047	0.975		0.131	0.179	0.464		0.037	1.058	0.972	0.004	0.060	0.186	0.749	0.022
BRIEF Teacher Rating: Metacognition (lower = better)	0.019	0.089	0.832	0.007	0.014	0.436	0.974	0.001	-0.198	0.144	0.169	-0.058	0.070	0.441	0.873		-0.040	0.064	0.527		0.173	1.390	0.901		0.299	0.248	0.245		0.187	1.405	0.894	0.016	0.090	0.261	0.729	0.027
Behavior Regulation (lower = better)																																				
CRS-R: Parent Rating: Hyperactive/Impulsive	0.003	0.019	0.853	0.006	0.079	0.087	0.364	0.030	0.000	0.028	0.998	0.000	0.065	0.093	0.488		-0.030	0.013	0.020+		-0.402	0.292	0.169		0.097	0.050	0.054		-0.323	0.296	0.275	-0.121	0.097	0.052	0.063	0.127
CRS-R: Teacher Rating: Hyperactive/Impulsive	0.020	0.022	0.367	0.029	-0.019	0.111	0.867	-0.006	-0.069	0.036	0.059	-0.079	-0.070	0.112	0.535		-0.025	0.016	0.113		0.124	0.355	0.726		0.177	0.063	0.005*		0.106	0.358	0.768	0.035	0.108	0.066	0.106	0.124
CRS-R: Parent Rating: Inattentive	0.010	0.022	0.638	0.014	0.025	0.101	0.807	0.008	-0.030	0.033	0.365	-0.033	0.040	0.109	0.713		-0.001	0.015	0.964		-0.165	0.341	0.628		0.008	0.059	0.898		-0.140	0.345	0.684	-0.045	-0.021	0.061	0.725	-0.024
CRS-R: Teacher Rating: Inattentive	0.001	0.029	0.984	0.001	0.009	0.142	0.950	0.002	-0.046	0.047	0.326	-0.042	0.026	0.144	0.858		-0.005	0.021	0.824		0.227	0.451	0.615		0.060	0.081	0.462		0.236	0.456	0.606	0.061	0.014	0.086	0.872	0.013
BRIEF Parent Rating: Behavior Regulation	-0.023	0.040	0.569	-0.018	-0.061	0.186	0.745	-0.011	0.075	0.060	0.214	0.046	-0.066	0.200	0.742		-0.033	0.028	0.237		-0.422	0.627	0.501		0.153	0.108	0.158		-0.483	0.634	0.446	-0.085	0.227	0.112	0.042*	0.139
BRIEF Teacher Rating: Behavior Regulation	0.029	0.048	0.540	0.020	0.186	0.234	0.426	0.029	-0.089	0.078	0.252	-0.049	-0.050	0.237	0.832		-0.017	0.034	0.621		0.063	0.749	0.933		0.180	0.133	0.178		0.249	0.756	0.742	0.039	0.091	0.141	0.521	0.050
Tics (lower = better)																																				
Motor tics (current): Assessor Rating	0.018	0.011	0.099	1.345	-0.038	0.069	0.580	0.864	0.031	0.024	0.190	1.510	0.047	0.066	0.478		-0.031	0.015	0.042+		0.047	0.195	0.810		0.064	0.040	0.110		0.009	0.199	0.966	1.033	0.095	0.042	0.025*	3.529
Phonics tics (current): Assessor Rating	-0.012	0.019	0.533	0.825	0.032	0.074	0.661	1.132	0.032	0.024	0.187	1.534	0.026	0.062	0.673		-0.005	0.011	0.651		0.131	0.188	0.486		0.023	0.040	0.566		0.163	0.194	0.400	1.867	0.055	0.041	0.184	2.078
Motor tics (current): Parent Rating	0.003	0.012	0.795	1.055	-0.106	0.070	0.129	0.666	0.009	0.022	0.681	1.130	-0.040	0.103	0.700		-0.013	0.010	0.213		-0.086	0.289	0.765		-0.004	0.041	0.931		-0.192	0.290	0.508	0.479	0.006	0.043	0.895	1.078
Phonics tics (current): Parent Rating	-0.013	0.017	0.437	0.807	0.030	0.065	0.638	1.123	0.011	0.020	0.605	1.150	-0.101	0.102	0.323		0.010	0.008	0.209		0.104	0.219	0.633		-0.045	0.037	0.220		0.135	0.223	0.545	1.674	-0.035	0.039	0.370	0.630
General Intellectual Functioning																																				
WASI Verbal IQ	0.054	0.047	0.247	0.031	-0.399	0.220	0.071	-0.052	-0.014	0.071	0.840	-0.007	-0.128	0.236	0.587		-0.006	0.033	0.859		-0.242	0.755	0.749		0.102	0.128	0.426		-0.641	0.763	0.401	-0.084	0.087	0.132	0.510	0.040
WASI Performance IQ	-0.009	0.054	0.875	-0.005	0.304	0.254	0.231	0.038	0.114	0.080	0.158	0.050	-0.167	0.269	0.534		-0.016	0.037	0.668		0.328	0.844	0.697		-0.024	0.147	0.870		0.632	0.855	0.460	0.079	0.090	0.152	0.554	0.039
WASI Full Scale IQ	0.027	0.049	0.580	0.015	-0.082	0.227	0.717	-0.011	0.075	0.074	0.310	0.034	-0.137	0.240	0.570		-0.008	0.033	0.804		-0.135	0.766	0.861		0.015	0.131	0.908		-0.217	0.774	0.779	-0.028	0.090	0.137	0.510	0.041

Key: Mercury effect = Better Outcome — < .05: p-value* — >.05, <.10: p-value

Mercury effect =Worse Outcome — < .05: p-value* — >.05, <.10: p-value

P-values shown are rounded to 3 decimal places. Therefore, a value shown as 0.050 may satisfy p<0.05 criterion if the original value was rounded up, or may not satisfy the criterion if the value was rounded down.

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