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Review

Empirical Data Confirm Autism Symptoms Related to Aluminum and Acetaminophen Exposure

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Abstract: Autism is a condition characterized by impaired cognitive and social skills, associated with compromised immune function. The incidence is alarmingly on the rise, and environmental factors are increasingly suspected to play a role. This paper investigates word frequency patterns in the U.S. CDC Vaccine Adverse Events Reporting System (VAERS) database. Our results provide strong evidence supporting a link between autism and the aluminum in vaccines. A literature review showing toxicity of aluminum in human physiology offers further support. Mentions of autism in VAERS increased steadily at the end of the last century, during a period when mercury was being phased out, while aluminum adjuvant burden was being increased. Using standard log-likelihood ratio techniques, we identify several signs and symptoms that are significantly more prevalent in vaccine reports after 2000, including cellulitis, seizure, depression, fatigue, pain and death, which are also significantly associated with aluminum-containing vaccines. We propose that children with the autism diagnosis are especially vulnerable to toxic metals such as aluminum and mercury due to insufficient serum sulfate and glutathione. A strong correlation between autism and the MMR (Measles, Mumps, Rubella) vaccine is also observed, which may be partially explained via an increased sensitivity to acetaminophen administered to control fever.

Keywords: autism; vaccines; MMR; HEP-B; glutathione; sulfate; cholesterol sulfate; aluminum; mercury; acetaminophen

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1. Introduction

Autism, and, more broadly, autism spectrum disorder (ASD), is a condition characterized by impaired cognitive and social skills [1], along with a compromised immune function [2–5]. It can now no longer be denied that the incidence of ASD is alarmingly on the rise in the U.S. [6]. While it has been suggested that the observed increase in rates may be due mainly to a change in diagnosis criteria, the actual criteria have changed very little from 1943 to DSM-IV-TR [7–9]. Despite considerable research efforts devoted to trying to uncover the cause(s) of autism, thus far no definitive answer seems available from the research literature. However, the fact that ASD rates have been rapidly increasing over the last two decades strongly points to an environmental component. Indeed, autism is recently being reframed from being a strictly genetic disease to representing a complex interaction between genetics and environmental factors, suggesting that we should focus our attention more on "environmentally responsive genes" [10].

The ASD community has maintained a long-standing conviction that vaccination plays a causative role in ASD [11], an idea that has been vehemently denied by the vaccine industry [12], but nonetheless is still hotly debated [13]. A study published in 2011 has confirmed a positive correlation between the proportion of children who received vaccinations in each state over the interval from 2001 to 2007 and the incidence of autism or speech and language impairment [14]. For each 1% increase in vaccination rate, 680 additional children were diagnosed with autism or speech delay.

In [15], we proposed that a causative factor in autism is an inadequate supply of cholesterol sulfate, both *in utero* and postnatally. Cholesterol sulfate synthesis in the skin is catalyzed by sun exposure [16]. We hypothesized that autism may be induced by a combination of inadequate dietary sulfur and insufficient sun exposure to the skin, for both the mother and the child. A meta-study involving oxidative-stress related biomarkers present in association with autism identified a consistent deficiency in reduced glutathione [17], an important sulfur-based antioxidant that also plays a role in detoxifying aluminum. We proposed that cysteine, the rate-limiting amino acid involved in the synthesis of glutathione [18], is depleted through redirection into an alternative pathway to produce sulfate, due to the impaired sulfate synthesis from thiosulfate in the skin.

A recent study of biomarkers for 28 individuals with an ASD diagnosis showed reduced glutathione, cysteine, and sulfate compared to controls, and the authors proposed that a reduced detoxification capacity might impede mercury excretion [19]. These same authors observed a marked reduction in serum sulfate in association with ASD in another paper [20]. In particular, the level of free sulfate in the blood stream was only 33% of the level found in control subjects. We hypothesize that sulfate deficiency results in insufficient ionic buffering in the vasculature, with grossly inadequate sulfation of the extracellular matrix proteins that are essential for proper colloidal suspension of particles and cells [21,22].

Glutathione [23] and sulfate [24] are also essential for the detoxification of xenobiotics and commonly administered drugs like acetaminophen in the liver. Selenium, a trace metal in the same column of the periodic table as oxygen and sulfur, has been shown to protect against acetaminophen toxicity [25], and it has also been shown to be severely depleted in hair and nail samples from individuals on the autism spectrum [26].

A possible link has been found between acetaminophen and both autism and asthma [27]. The association of both asthma [28] and eczema [29] with ASD can be explained as an inadequate supply of filaggrin, due to the fact that cholesterol sulfate in the epidermis stimulates the production of profilaggrin, its precursor [30]. Filaggrin plays an essential role in maintaining the epithelial barrier [31], and its impairment leads to increased risk of both asthma [32] and eczema [33,34]. Thus cholesterol sulfate deficiency provides an explanation for the multiple links among autism, acetaminophen, asthma, and eczema.

It has been demonstrated that chronic aluminum exposure in rats induces depletion of glutathione in the liver as well as a significant reduction in the synthesis of bile acids [35], which are conjugated with taurine, the only sulfonic amino acid [36]. Taurine administration in conjunction with aluminum greatly ameliorates the adverse effects of aluminum on the liver, and this was explained as possibly due to the ability of the sulfonate group in taurine to bind with heavy metals such as aluminum [37]. These results suggest that glutathione and taurine are both involved in aluminum detoxification in the liver.

Many children with autism have a low amount of serum glutathione, with a larger fraction of it oxidized to GSSG [38]. Furthermore, increased use of antibiotics leads to an alteration in gut flora which impairs the ability to detoxify toxic metals like mercury. Dimercaptosuccinic acid (DMSA), an organosulfur compound with two thiol groups, has been found to be effective in ameliorating the symptoms of autism in placebo controlled studies [39], likely through its ability to enable the excretion of toxic metals such as lead and mercury [40]. It also led to a normalization of glutathione levels in red blood cells [40].

Vitamin D deficiency has been hypothesized to be a risk factor for autism [41]. The over-zealous application of sunscreen is strongly implicated in autism, not only because sunscreen interferes with the production of vitamin D_3 and cholesterol sulfate but also because it often contains aluminum, particularly the high Sun Protection Factor (SPF) sunblock products. Aluminum, due in part to its +3 ionic charge, is highly toxic to biological systems [42,43] as will be described more fully in Section 2.1. Indeed, there are no known life forms that utilize aluminum in any biological systems. The poorly developed barrier function of the autistic child's epidermis would likely lead to an increased penetration of aluminum through the skin. Furthermore, their serum sulfate deficiency leads to an impaired ability to dispose of aluminum. Aluminum would therefore be expected to accumulate over time, and, due to increased permeability of the blood brain barrier associated with autism [44], would almost certainly interfere with neuron function.

In the next section, we examine the evidence from the literature that aluminum toxicity may play a role in vaccine adverse reactions, and we describe available theories for the mode of toxicity of aluminum and other toxic metals.

2. Aluminum and Mercury in Vaccines

It has recently been proposed that aluminum, commonly used in vaccines as an adjuvant, may be the most significant factor in adverse reactions, and, furthermore, that the nervous system is especially vulnerable to aluminum toxicity [45]. Vaccine clinical trials often include aluminum in the placebo, at the same or greater concentrations than the amount found in the vaccine [46–49]. A comparable number of adverse reactions between vaccine and placebo in these trials suggests that aluminum is an important source of toxicity in the vaccine. Indeed, intraperitoneal injection of aluminum-adsorbed vaccine in mice caused a transient rise in aluminum in brain tissues [50].

The Food and Drug Administration (FDA) has set an upper limit of 5 micrograms Al/kg/day for neonates and individuals with impaired kidney function [51]. A highly informative recent review of a possible relationship between aluminum toxicity and Alzheimer's disease [52] also discussed issues related to the aluminum burden in children's vaccines. There, it was pointed out that children today receive a cumulative aluminum burden from vaccines that may exceed the FDA limit by a factor of 50.

The vaccine industry has a difficult task in designing vaccines that are both safe and effective [53]. The use of weakened but live pathogens can lead to vaccine-induced disease in children with an impaired immune system, yet debris from *dead* pathogens may not always cause a sufficient reaction to induce the production of antigen-specific memory CD8 T-cells, required for protection against future exposure. The industry widely reports success in creating vaccines with dead pathogens by adding adjuvants such as aluminum, lipopolysaccharide (LPS) from *E. coli*, and polycationic surfactants, to further stimulate the immune response [54]. It remains unclear exactly how aluminum achieves its effect of enhancing the immune reaction, but aluminum adjuvants are now thought to impact on humoral systems via their positive influence on the inflammasome complexes [55].

Another industry-claimed basis for adding aluminum or mercury to vaccines is to increase the stability of the antigen in long-term storage. It has been shown that the rate of acid-catalyzed hydrolysis of glucose-1-phosphate is significantly slower when the molecule is adsorbed to aluminum hydroxide adjuvant, increasing the effective pH of the environment by 2 pH units [56]. This effect would however also interfere with the human body’s ability to break down the antigen from the vaccine, which may partially explain the heightened immune reaction.

Based on concerns that the mercury (49.6% by weight) in thimerosal might be contributing to autism [57], the industry made an effort to significantly reduce the amount of mercury present in vaccines beginning in the late 1990’s [58]. In parallel, they began storing the vaccines in individualized glass vials—to avoid the ostensible need for a preservative to reduce the danger of contaminating repeated invasions of multidose vials. However, this raises another concern, as aluminum can be leached out of the glass vial and the rubber stopper during storage [59]. This same issue can also affect premature infants given serum albumin infusions, resulting in an inadvertent exposure to aluminum very early in life [60].

Glass contains aluminum oxide at levels ranging from 1.9% to 5.8% [61]. Leaching from a container is an ongoing process until the product is used. Storage containers contribute significantly to aluminum contamination in human serum albumin products. Because of impaired renal function, dialysis patients are at risk to developing encephalopathy and a severe form of dementia due to their inability to dispose of the small amounts of aluminum that could be present in the dialysis water base [62],

although this problem has been largely corrected today. We suggest that the effect of aluminum on the brain of a person already on the autism spectrum may manifest a similar pathology.

Mechanisms of Aluminum and Mercury Toxicity

Aluminum is one of the most common elements on Earth, yet no biological system has yet found a use for it. Aluminum is expected to induce biosemiotic entropy through multiple pathways [22,63,64]. Its +3 charge and highly kosmotropic properties make it extremely destructive in water-based biological systems. One purely biophysical mechanism might involve its direct effect upon interfacial water tension. Another less direct mechanism might involve competition for calmodulin binding and the initiation of a signaling cascade with profound consequences. Both phenomena would likely induce biosemiotic entropy through both supramolecular and epigenetic effects. Thus, a focus limited solely to genetics and molecular biology is likely to be misguided. Long-range, dynamically-structured interfacial water is the medium which, when energy-loaded, both conveys the biological message and overcomes the thermal diffusion problem [65,66]. When interfacial water is energy-unloaded, the biological message is corrupted: unfolded protein responses and apoptosis follow. We posit that aluminum is a *sine qua non* of biosemiotic entropy—an exogenous interfacial water stressor.

Since aluminum is a known neurotoxin, there is no safe level. The central nervous system is particularly susceptible to the deleterious effects of aluminum. Exposure of human neuronal cells to a low concentration (100 nM) of aluminum sulfate induces a response that emulates the gene expression changes associated with Alzheimer's disease [67]. Recently, a group of researchers investigated the effect of aluminum sulfate on an *in vitro* culture of human neural cells [63], which was directly compared to the effect of magnesium-, iron- and zinc sulfate. They confirmed that, by contrast with the other salts, aluminum sulfate had an unusual and significant ability to induce NF-κB signaling and subsequent reactive oxygen species (ROS), mediated by down-regulation of the important inflammation inhibitor, complement factor H (CFH). In a subsequent paper, the sulfates of 13 different cations were assessed for their ability to induce ROS in neuronal cultures, and aluminum was determined to stand out among all the ions studied for its remarkable ability to induce ROS, even compared with mercury and lead [64]. Aluminum induced a response that was a factor of seven higher than that of mercury and a factor of three higher than that of lead.

Aluminum adjuvants damage and rupture the phagolysosomes, generate reactive oxygen species, and induce potassium efflux from the cell [68]. Our research has led us to suspect disruption of calmodulin (CaM) signaling as one of the most destructive aspects of aluminum toxicity. CaM functions as a calcium sensor and signal transducer that regulates a number of distinct protein targets, influencing many different cellular functions [69]. Upon binding to calcium, CaM undergoes a conformational change, and subsequent transformations such as phosphorylation, acetylation, and methylation can modulate its action.

The aluminum ion is a potent inhibitor of voltage-gated calcium channels in the brain [70]. Normally, calmodulin (CaM), after binding to calcium, stimulates nitric oxide (NO) production by both endothelial nitric oxide synthase (eNOS) and neuronal nitric oxide synthase (nNOS). An investigation of the interaction of aluminum ions with bovine brain CaM [71], confirmed that aluminum binds to CaM with an affinity that is an order of magnitude stronger than that of calcium.

Interaction with aluminum induces a conformational change in the molecular structure. A molar ratio of 4:1 for aluminum/CaM completely blocks the activity of CaM-dependent phosphodiesterases. Highly hydrated aluminum ions profoundly influence the protein's flexibility and disrupt its structural integrity.

Severe impairment of astrocyte function has been demonstrated in conjunction with aluminum exposure [72,73]. Aluminum appears to interfere with iron-sulfur clusters in the mitochondria, causing impaired ATP synthesis, excess production of reactive oxygen species, and impaired formation of the cytoskeleton, which is essential for the cell's function in maintaining the health of neighboring neurons. Cells exposed to as little as 0.01 mM concentrations of aluminum show a disrupted actin cytoskeleton and a drastic morphological change into a globular configuration. Due to its cationic +3 charge, aluminum directly causes in vitro aggregation of neurofilaments characteristic of many human neurological diseases [42].

NO Synthesis by eNOS after aluminum exposure: An excessive production of NO can result in anaphylactic shock, a life-threatening allergic reaction, associated with overexuberant vasodilation and a precipitous drop in blood pressure. A recent experiment with mice triggered anaphylactic shock by exposing the mice to an injection containing aluminum hydroxide and pertussis toxin [74]. This resulted in the excess synthesis of NO by eNOS, and a subsequent signaling cascade, mediated by the phosphatidyl inositol-3 kinase (PI3K) pathway. We hypothesize that aluminum's propensity to bind strongly to CaM mediated this response.

Aluminum's Effects on Neurons: A novel characteristic of the autistic brain is that it is larger than the non-autistic brain at the age of two or three [75], an effect that is hypothesized to be due to an impaired glutamate-mediated neuronal-pruning developmental phase. Overgrowth is observed in cerebral, cerebellar, and limbic structures underlying cognitive, social, emotional, and language functions [76]. Significantly, a study involving prenatal aluminum exposure revealed an effect on neurons in rat brains suggesting resistance to apoptosis following glutamate signaling, a potentially related phenomenon [77]. Glutamate-induced neuronal death was significantly reduced in primary cultures of cerebellar neurons taken from aluminum-exposed rats. The effect was shown to be mediated by a disruption of CaM signaling to induce nNOS activity, analogous to the CaM-related effect of aluminum in endothelial cells.

Aluminum and Mercury Impact Zeta Potential and Sulfate Recycling: Zeta potential (ZP) is defined by the rate at which a charged particle suspended in a medium will travel in an applied electric field. A high negative value for zeta potential is essential for maintaining blood as a colloidal suspension [21]: cells and complex molecules suspended in the blood avoid flocculation through a negative charge field maintained in the immediate surrounding space. One of the main functions of serum albumin is to control colloid stability in the blood [78].

Both mercury and aluminum bind strongly to cysteines in serum albumin in the blood stream [79,80]. The adsorption of aluminum onto serum albumin has a profound effect on serum zeta potential (ZP) [80], driving it even to positive values at physiological pH with sufficient concentrations of aluminum hydroxide. It is believed that much of the mercury that is filtered into the proximal tubular lumen in the glomerulus of the kidney is present primarily as a conjugate of albumin, bound to the sulfhydryl group of a cysteine constituent [79]. Thus, positively-charged mercuric Hg^{2+} salts bound to serum albumin would be expected to cause a similar effect as aluminum on serum ZP.

Mercury has a great predilection for bonding to reduced sulfur atoms, especially those in thiol-containing molecules such as glutathione, cysteine, homocysteine, and albumin. The affinity of mercury towards oxygen-or nitrogen-containing ligands is about 10 orders of magnitude lower [79]. A study on oral exposure to methylmercury in mice confirmed that the methylmercury is absorbed, taken up by the liver, and then exported via the bile acids, likely bound to bio-organic sulfate. These researchers demonstrated a complete inability to dispose of methylmercury in neonate animals, confirming that newborns are much more susceptible to mercury toxicity than adults [81]. It was shown that this impaired disposal was due in part to insufficient glutathione in the liver.

A study on infant monkeys confirmed that the ethylmercury in thimerosal that is injected into the primate is more readily stored as inorganic mercury in the brain than is orally-delivered ethylmercury, and that inorganic mercury tends to linger longer in the tissues [82]. Exposure to thimerosal leads to abnormal glutamate transport in neurons in mouse hippocampi [83]. Mercury also has an adverse effect on sulfate recycling in the glomeruli, leading to a net loss of sulfate via the urine. A noticeable reduction in the production of dermatan sulfate is associated with mercury exposure, via an effect on the mesangial cells [84]. Thus, mercury would be expected to either build up to toxic levels or further reduce sulfate bioavailability in the child with autism**.**

3. Related Work

3.1. MMR Vaccine

It has been suggested that the measles, mumps, and rubella (MMR) vaccine may be contributing to the increased prevalence of autism in recent decades [85]. A large population-based study involving children born in Denmark between 1991 and 1998 has seemingly proven otherwise [12]. In comparing 440,000 vaccinated children with 96,000 unvaccinated children, the authors claimed that no significant difference in the incidence of autism was detected between the two groups. However, there are several concerns with this study. The first one is that the reasons for not vaccinating were not determined, and it is likely that important reasons might have been the presence of autism in a close family member, thus predisposing the non-vaccinated population to autism due to the inheritability of the disease (or, the fact that the mother still has the nutritional deficiency that caused the older sibling's autism). Another possibility for exclusion is an actual diagnosis of autism, or an adverse reaction to some other vaccine, a feature that is also likely associated with increased risk of autism.

The second concern has to do with the way the data were analyzed. It would seem to be logical to divide the 0–3 age group into two subsets, one before 15 months and one after 15 months, in order to more easily assess the relevance of MMR (administered at 15 months) to the autism diagnosis. But the authors chose to combine all cases under 3 into a single category in the summary table they presented in the paper. Furthermore, any diagnoses before 15 months were inexplicably put into the "not-vaccinated" group, whereas they should have simply been excluded. The non-vaccinated group had, relatively speaking, more diagnoses before three years, but some unknown percentage of these, possibly even all of them, occurred before the 15-month cut-off.

By contrast, substantially fewer cases of autism were diagnosed in the window between 3 and 5 years in the *not*-vaccinated group, if the two populations are distributed equally by age. From the

numbers in their table, one can compute a 41% increased relative frequency of autism diagnosis in the vaccinated versus the unvaccinated population in this age range, a number that might well have been statistically significant had it been singled out.

Finally, it is likely that other vaccines in addition to MMR play a role in autism, particularly since, unlike many vaccines, MMR contains neither thimerosal nor aluminum. MMR is often administered simultaneously with DTaP, an aluminum-containing vaccine. The synergistic and cumulative effects of multiple vaccines would likely lead to nonlinear enhancement of adverse events.

It has been claimed that Denmark had excluded thimerosal from all vaccines prior to the birth of any of the children in the study [86]. If this is true, then this is in stark contrast to the U.S. policy, where thimerosal still appears in several vaccinations given to young children, including Hep-B and HiB Titer. Aluminum is present in several of the vaccines, for example, Hep-B, PREVNAR, all of the DTaP formulations, and H1N1 flu vaccine multidose vials.

3.2. Other Related Work

Aluminum adjuvants are the only adjuvants approved for use. They are known to enhance the specificity, intensity, and duration of the immune response, leading to improved long-term protection from the disease [87]. A workshop was held in 2002 in San Juan, Puerto Rico, addressing the issues associated with aluminum in vaccines, with a particular focus on myalgias and fatigue in adults following vaccination exposure to aluminum [88]. A recently published article seriously addresses the question of the safety of aluminum adjuvants in vaccines, pointing out the neurotoxicity of aluminum [45]. A U.S.-based study published in 2010 [89] determined that a three-fold increased risk to autism was associated with neonatal administration of Hepatitis B (Hep-B) vaccine prior to 1999, compared with either no vaccination or a delay until after the first month of age. Notably, Hep-B contains both aluminum and mercury.

Several researchers have reported increased frequencies of either sudden death or other health crises such as anaphylaxis or cardiorespiratory problems in association with vaccines. In [90], it was reported that six infants died suddenly within 48 hours of having received a hexavalent vaccine, a frequency that is abnormally high compared to the risk of SIDS in the general population. Unexpectedly high SIDS rates following vaccination are also reported in [91]. Researchers in Italy [92] report that the first vaccination carries an increased risk to SIDS in infants. In [93], through statistical analysis based on 300 cases of unexplained sudden death, a 16-fold increased risk was determined following the fourth dose in a series of vaccinations. In [94], it was reported that the observed rate of anaphylaxis following administration of the HPV vaccine to females aged 12 to 26 was significantly higher than the rate observed following other vaccines. In [95], precautionary monitoring is recommended following vaccination of premature infants, due to observed adverse reactions related to cardiorespiratory events, as well as a substantial increase in serum levels of C reactive protein, an inflammatory marker. This was particularly true for DTaP, an aluminum- containing vaccine, especially when it was combined with concomitant vaccines.

Goldman and Miller [96] have previously examined the VAERS database, specifically looking at hospitalization rates and mortality statistics as a function of the number of vaccines simultaneously administered and of age. Linear regression analysis revealed several statistically significant trends,

including a positive correlation between hospitalization rates and number of vaccine doses. In addition, mortality rates for infants under six months were significantly higher than rates for children between six months and one year of age, suggesting increased sensitivity of neonates. The authors suggested delaying administering of vaccines as a strategy for reducing risk of a severe adverse reaction. These authors also emphasize the value of VAERS as an important postmarketing safety surveillance tool.

Studies on adverse reactions for vaccination of adults have also been performed. A 2002 study of the VAERS database related to Hepatitis B vaccine confirmed a significant number of adverse reactions in adults [97]. A case study published in 2009 described an adult's profound adverse reaction to multiple vaccinations containing aluminum, resulting in aluminum hydroxide deposits accumulating in macrophages in muscle cells, along with debilitating muscle pain and weakness associated with chronic fatigue syndrome and macrophagic myofasciitis [98].

4. Our Studies with U.S. CDC VAERS Database

The Vaccine Adverse Event Reporting System (VAERS) is a surveillance system implemented by the U.S. government, which allows doctors and/or patients to report any adverse reactions observed in association with vaccines. The cover page emphasizes that the data report only an association rather than a confirmed causal relationship. Data are readily available for download from the web site, "http://vaers.hhs.gov/index" beginning in the year 1990. In this section, we will present the results of several experiments we conducted with the VAERS database, using standard statistical techniques based on word frequency information.

In order to validate our methods, we first examined the differences between a set of records associated with autism and a comparison set drawn randomly from the remaining records. The autism-related data set contained all cases where the word "autism" or the word "autistic" showed up somewhere in the report. This yielded a total of 1,734 entries. The comparison set was constructed by randomly sampling from the remaining entries (~340,000 reports), but in such a way that the age distribution was exactly matched to the distribution obtained from the records associated with autism, obtaining a record of identical size (1,734) to that of the autism set. We performed a statistical analysis of selected words and phrases in the "symptom text" field as well as in the five "symptoms" fields in the associated VAERSSYMPTOM files.

We used an established method based on log likelihood ratio, as described in [99,100], which provides a *p*-value associated with the likelihood that the observed distribution bias of the word or phrase could have occurred by chance. To improve statistical power, we collected the most frequently occurring words in the "symptoms" fields, and organized them into reasonable classes. For example, "abdominal pain," "abdominal discomfort," "abdominal distention," and "abdominal tenderness" collectively represented the class "abdominal pain."

Table 1 shows all of the words or phrases that were biased towards the autism data set with a *p*-value at or below 0.05. Constipation [101], anxiety [102], asthma [28], eczema [29] and premature birth [103] have all been found to be associated with autism in the research literature. We consider it to be a validation of our methods that we detected these features with a statistically significant *p*-value. This also implies that the VAERS database may be useful for predicting associations between symptoms and conditions, irrespective of any claim about the effects of a particular vaccine.

Prematurity would be expected to be a risk factor for ASD, as the cholesterol sulfate supply from the placenta is normally greatly increased toward the end of pregnancy [104]. Premature infants may also suffer from additional aluminum exposure through albumin infusions [60].

Table 1. Skewed distributions of symptom words between two data sets: a set of vaccine adverse reactions associated with autism, and an age-matched set of other vaccine reactions. C1: number of entries in autism set containing this symptom; C2: Number of entries containing this symptom in the comparison set. *p*-value: the likelihood that the distribution would have occurred by chance according to a log-likelihood ratio formulation.

Symptom	C1	C2	*p*-value
Anxiety	49	2	0.011
Constipation	41	0	0.012
Infection	54	6	0.013
Ear infection	32	3	0.029
Eczema	18	0	0.044
Premature	20	1	0.046
Asthma	24	3	0.048
Pneumonia	19	1	0.050

Note: In this and subsequent tables, we use the word "symptom" inclusively to refer to signs, symptoms and conditions.

Three associated words suggestive of a weakened immune system, "infection," "ear infection," and "pneumonia" support the observation from the literature that autism is associated with immune dysfunction [2]. It has also been demonstrated that children with the autism diagnosis exhibit a heightened immune response to antigen stimulation [105], which we propose is caused by their global deficiency in sulfate supply. Thus, their increased vulnerability to infection in general likely parallels an increased likelihood of an adverse reaction to vaccines, particularly vaccines like MMR where the pathogen is only weakened but not killed.

4.1. Distribution of Vaccine Types in Autism versus Controls

Another aspect we investigated from the VAERS database is to compare the distribution of type of vaccine administered between the autism-related events and the non-autism-related events. The results are shown in Table 2. We looked only at data for children under 6 years old, and we computed the percentage of events associated with each vaccine type in each data set. As shown in Table 2, MMR was significantly more likely to be associated with autism (41% of the autism-associated events as against only 15% of the non-autism associated events, with a ratio of 2.67). HiB Titer and hepatitis were also over-represented in the autism group, although to a lesser degree.

Since MMR contains neither aluminum nor mercury, it is puzzling that children with the autism diagnosis seem to be highly sensitive to it. We have not examined the records in detail to determine what percentage had autism before receiving the vaccine, and, in fact, in many cases this information is not available from the VAERS record, which may simply list autism as a feature. An interesting theory relating the MMR vaccine to ASD involves a proposed toxic reaction to the acetaminophen (paracetamol) administered to control fever following vaccination [25,106]. It has been proposed that

acetaminophen may mediate oxidative stress and neurotoxicity in autism [107], and acetaminophen has been demonstrated to be toxic to developing mouse cortical neurons *in vitro* [108].

Table 2. Percentages of events associated with different vaccine types in the autism data set versus the not autism data set, and the ratio between the two. The numbers add up to more than 100% due to the fact that multiple vaccines are often simultaneously administered.

Pathogen	Percent Autism	Percent Not Autism	Ratio
MMR	40.94	15.35	2.67
Hep-B	16.02	8.71	1.84
HiB Titer	15.02	8.40	1.80
DTaP	42.53	43.93	0.97
Polio	15.60	16.34	0.96
Varicella	15.77	16.68	0.95
Pneumonia	8.81	10.29	0.86
Rotavirus	0.25	3.29	0.076
Total	**154.94**	**122.99**	**1.26**

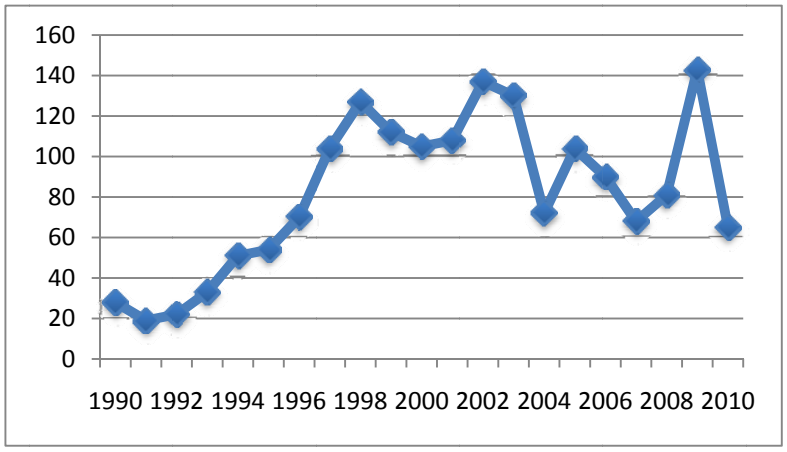
A study of the ability of children with the autism diagnosis to dispose of paracetamol found that the ratio of paracetamol-sulfate to paracetamol-glucuronide (PS/PG) in the urine of children with severe autism following acetaminophen administration was significantly lower ($p < 0.00002$) than that measured for normal controls [109]. This result strongly suggests an impaired ability to metabolize toxic substances via a sulfation pathway. If the MMR vaccine is administered simultaneously with DTaP, an aluminum-containing vaccine (as is often the case), then the acetaminophen would likely interfere with the child's ability to dispose of the aluminum.

The autism-associated events exhibited an 84% increased frequency of reactions to hepatitis, and an 80% increased frequency of reactions to HiB Titer. While we included both Hep-A and B in the search, the matches were almost exclusively to Hep-B. Hep-B contains aluminum hydroxide and thimerosal, and HiB Titer contains thimerosal.

Hep-B is administered usually within 24 hours of birth, and most definitely in the first two months of life, and HiB Titer is administered three or four times before the age of 15 months. These two vaccinations would thus cause an accumulation of mercury and aluminum along with a depletion of the bioavailability of sulfate prior to the MMR vaccine in the vulnerable child, leaving them more susceptible to an infection arising from the live virus administered in MMR, and a subsequent dose of Tylenol (acetaminophen) to curb fever.

Another aspect we investigated was the number of events associated with autism as a function of the year the event was reported. Realizing that the report date and the event date can sometimes be separated by several years, we reported this detailed profile over time based on the event date instead of the report date. In cases where the event date was unavailable, we used the report date instead. The results are shown in Figure 1. It is striking that the number rises steadily over the last five years of the twentieth century, peaking around 2003. In the U.S., aluminum was allegedly phased in at the same time that mercury was phased out [110]. If the current CDC immunization schedule [111] is followed, babies are injected with nearly 5 mg of aluminum by 18 months of age.

Figure 1. Number of adverse events in VAERS where the word "autism" or "autistic" was mentioned in at least one of the fields in the record, plotted as a function of the year in which the event occurred, from 1990 to 2010. For cases where the event year was not available, we used the year of the report instead.



Given that autism incidence in the VAERS database continued to rise after a small dip around 2000, and given the knowledge that the total thimerosal burden had been significantly reduced by that time, we developed the hypothesis that an enhancement of aluminum adjuvant in the vaccine might have been the reason for the observed continued high rates of autism. Mercury was phased out of vaccines around 1999 [110]. However, four doses of a new aluminum-containing pneumococcal vaccine were added to the vaccine schedule within the next few years [110,111], increasing the total aluminum burden by 20%. This could have masked any drops in autism rates consequential to the decreased mercury burden.

4.2. Relationship between Aluminum in Vaccines and Symptoms

In this next set of experiments we first collected all of the adverse events reported prior to 2000 (*i.e.*, for all age groups), and we collected an age-matched subset of all of the incidents that were reported after 1999. We performed our word frequency counts on these data, and discovered a large number of symptoms that were far more prevalent after 1999, as illustrated in Table 3.

We then collected two subsets of incidents that were reported any time between 1990 and 2010, one that included at least one aluminum-containing vaccine, and the other including only non-aluminum-containing vaccines. Specifically, "w/ aluminum" was defined as including a "vax name" that contained any of the following substrings: "DTAP", "DTP", "HEP", "PREVNAR", "HPV" or "ANTHRAX". For the "w/o aluminum" class, we eliminated any that contained these strings, as well as the strings "HIB" or "RABIES" as for this second experiment is also shown in Table 3.

For all of the symptoms in the table, and for both the before/after 1999 subsets and the w/, w/o aluminum subsets, all of the skewed distributions on counts were highly significant, thus strongly suggesting that aluminum-containing vaccines contribute to the increases in these symptoms. These symptoms, which are far more prevalent in the aluminum-containing vaccines, include severe reactions

such as seizure, cellulitis, cyanosis, depression, and even death. The alarming increase in seizures after 2000 is particularly disturbing in light of the known association between seizures and autism [44].

Table 3. Results of studies on adverse reactions over time, and as a function of aluminum contents of vaccines. The table shows selected reactions which were reported far more frequently in the "after-2000" subset than in the "before-2000" subset, with counts and *p*-values for both before/after 2000 and aluminum/non-aluminum containing vaccines. See text for details.

Symptom	C1 Before 2000	C2 After 2000	*p*-value	C1 w/ Al^{+3}	C2 w/o Al^{+3}	*p*-value
Seizure	636	3468	0.0000	2350	1023.2	0.00028
Injection Site Reaction	1961	4605	1.0E-8	3851	2584	0.000061
Infection	195	1552	1.0E-8	1358	927	0.0026
Swelling	8621	13218	1.0E-8	11406	8470	0.0000026
Pain	8153	12122	6.0E-8	8576	7099	0.00044
Cellulitis	760	1977	0.000001	2087	1089	0.000024
Depression	57	322	0.00023	334	143	0.0031
Death	210	558	0.0040	483	303	0.011
Fatigue	1222	1839	0.00080	1744	968	0.00011
Insomnia	81	195	0.0089	230	71	0.0025

In order to better characterize the set of symptoms that are associated with aluminum-containing vaccines, we computed a tally of the *total* number of mentions of every symptom whose word frequency was associated with aluminum-containing vaccines with a *p*-value less than 0.01. There were twelve such symptom classes, namely: fatigue, seizure, blister, cellulitis, pain, swelling, injection site macule, insomnia, injection site reaction, infection, depression, and uveitis. We compiled this statistic based on all *aluminum-containing* events in the database.

We then plotted a histogram over time of the result, to be compared with the plot of the histogram of autism mentions in the events. Results are shown in Figure 2. This plot shows a steady rise from about 1997 to 2003. It is conceivable that the workshop on aluminum held in 2002 [88] had some impact in reducing the aluminum burden in vaccines, although it is difficult to determine the adjustments of aluminum adjuvantion in vaccines over time, due to lack of transparency.

Figure 3 shows the *ratio* of the total number of aluminum-related *adverse reactions* associated with a particular year to the total number of aluminum-containing *events* occurring during that year. This number rises steadily over the turn of the century, reaching above 1.0 starting in the year 2000, and peaking at 1.4 in 2003. This means that multiple adverse reactions—cellulitis and reaction site macule, for example, are occurring in association with a single adverse event. The peak at 2003 corresponds well with the peak in autism-related reports. Thus there are introduced both an increase in the *number of events* around 2000 as well as an increase in the *potency* of each event to induce a reaction. This could be explained as an increased sensitivity to aluminum in the population, possibly due to a synergistic effect of cumulative exposure to multiple toxins [113].

Figure 2. Total count of symptoms in all the adverse events associated with aluminum-containing vaccines in VAERS whose word frequency is skewed towards events associated with aluminum-containing vaccines with a *p*-value less than 0.01, plotted as a function of year, from 1990 to 2010. Symptoms that met this requirement were: fatigue, seizure, blister, cellulitis, pain, swelling, injection site macule, insomnia, injection site reaction, infection, depression, and uveitis.

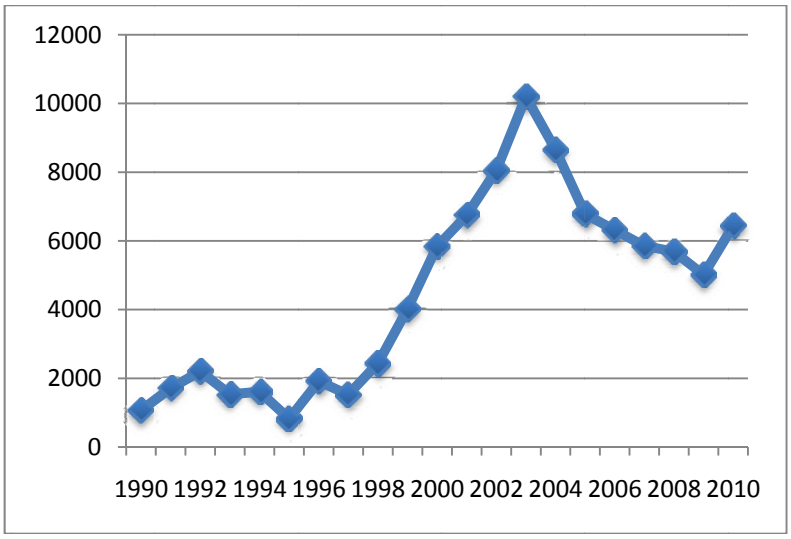
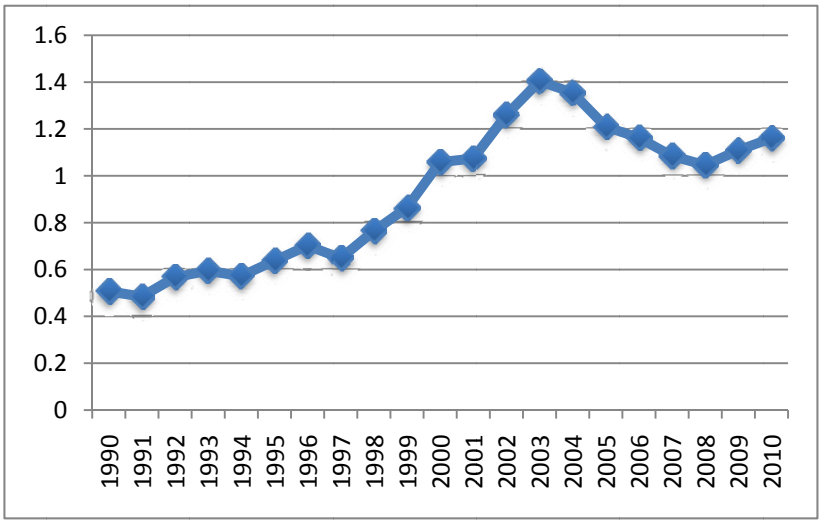


Figure 3. Total count of symptoms in all the adverse events associated with aluminum-containing vaccines in VAERS whose word frequency is skewed towards events associated with aluminum-containing vaccines with a *p*-value less than 0.01, plotted as a function of year, from 1990 to 2010, and *normalized* with respect to the *total* number of aluminum-associated adverse events occurring in that year. Symptoms that met this requirement were: fatigue, seizure, blister, cellulitis, pain, swelling, injection site macule, insomnia, injection site reaction, infection, depression, and uveitis.



4.3. MMR Vaccine and Autism

The occurrence of the feature "autism" in the vaccines with aluminum were somewhat, but not dramatically, higher than those without aluminum (556 with, 443 without; $p = 0.06$); *i.e.*, children with the autism diagnosis react to both aluminum-containing and non-aluminum-containing vaccines. We suspect this has to do with the impaired immune function in children with autism, which causes them to overreact to the MMR vaccine. Given that an adverse reaction to MMR is highly over-represented in the autism subset, we decided to compare a subset of the database where only the MMR vaccine had been administered with a comparably-aged subset where the MMR vaccine had *not* been administered.

The results are shown in Table 4. As might be expected, a diagnosis of infection with measles, mumps, or chicken pox were highly significantly associated with the MMR vaccine, as well as the simple word "rash" ($p = 0.00000003$). However, respiratory tract infection ($p = 0.042$) and cough ($p = 0.014$) were also over-represented in the MMR subset; suggesting that children with an infection are more likely to react adversely to the vaccine. Since children with the autism diagnosis have a compromised immune function, they are more likely to be sick at the time of the injection. But, most interesting for our purposes were the association of fever ($p = 0.024$) and autism ($p = 0.0067$) with MMR. There were a total of 1840 adverse reactions mentioning fever in the MMR set. This suggests to us that the acetaminophen connection may be correct—that the fever associated with MMR exposure is treated with acetaminophen, which then becomes toxic to the brain of the child predisposed toward autism, because of their inability to dispose of it. Acetaminophen would also deplete sulfate needed to detoxify aluminum in any concurrent aluminum-containing vaccine such as DTaP.

Table 4. Symptoms associated with MMR vaccine administered to children under six years old, with a *p*-value less than 0.05.

Symptom	C1 MMR	C2 not MMR	*p*-value
Rash	2197	745	3.0E-8
Chicken pox	311	23	6.6E-5
Mumps	217	0	0.00012
Face Oedema	232	28	0.00036
Measles	59	4	0.0089
Autism	168	58	0.0067
Cough	191	90	0.014
Fever	1840	1584	0.024
Hematoma	52	12	0.026
Conjunctivitis	42	7	0.027
Lymph Node Pain	25	0	0.028
Respiratory Infection	50	16	0.042
Blister	327	232	0.043

4.4. Hepatitis B Vaccine and Autism

An historical account of the introduction of mandatory vaccination at birth against Hep-B is presented in [114]. In 1991, the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control (CDC) recommended that all infants be injected with the first dose of hepatitis B

vaccine at birth. Since the states control mandatory vaccination policy, this recommendation was gradually put into law in nearly all of the states over the subsequent decade. By 1998, most children in America were required to show proof of three doses of Hep-B prior to entering public school. Since Hep-B contains both mercury and aluminum, and since it is administered at birth, it is likely to be a major factor contributing to the steady rise in autism-related events in the latter half of the 1990's.

The practice of requiring Hep-B administration *at birth* is likely to be extremely dangerous to children who are born with a sulfur deficiency. Furthermore, Hep-B booster shots are often administered in conjunction with the varicella vaccine (chicken pox). Children with a compromised immune system can respond to the live varicella vaccine by coming down with full blown chicken pox, and the infection in turn leads to increased vulnerability to the aluminum contained in the Hep-B vaccine.

Table 5. Symptoms associated with Hep-B vaccine administered to children under six years old, with a *p*-value less than 0.05. The values obtained for aluminum over all age groups are shown on the right for comparison purposes. The two symptoms at the top were not statistically significantly associated with aluminum, and are likely attributable to the compounding effect of the simultaneously administered varicella vaccine.

Symptom	C1 Hep-B	C2 not Hep-B	*p*-value	C1 w/ Al^{3+}	C2 w/o Al^{3+}	*p*-value
Rash	818	299	4.2E-5	11649	11109	-
chicken pox	80	3	0.0038	523	1152	-
Autism	108	1	0.0014	556	443	0.06
Macule	163	75	0.016	4702	3098	0.000016
Cellulitis	56	6	0.012	2087	1089	0.000024
Blister	188	53	0.0030	4275	3066	0.00015
Seizure	179	115	0.051	3331	2350	0.00028
Infection	78	12	0.0085	1358	927	0.0026
Abscess	74	26	0.029	1205	918	0.012
Death	38	6	0.030	483	303	0.011
Low appetite	32	2	0.025	368	252	0.031

Motivated by these arguments, we decided to compare vaccinations that include Hep-B with those that do not, over the age range from zero to six. Table 4 shows results for all symptoms with a *p*-value less than 0.05. The counts and *p*-values we obtained for aluminum are shown alongside the results for Hep-B for easy comparison.

These results are a little hard to interpret because there is a mixture of responses to Hep-B, responses to the associated varicella, and compounded responses. However, we can plausibly assume that "rash" and "chicken pox" are primarily due to varicella. "Infection" shows up significantly in both the Hep-B and the aluminum columns. This reflects the fact that an associated infection (whether a simple cold or the chicken pox or something else) increases the risk to aluminum toxicity, due to the additional burden on the immune system.

All of the significant symptoms in the table—macule, cellulitis, blister, seizure, abscess, death, and low appetite—are also significant symptoms associated with the vaccines containing aluminum. This

result further supports the possibility that the aluminum in these vaccines administered to young children may be even more toxic than the mercury.

A highly significant correlation is found between "autism" and "Hep-B" ($p = 0.0014$), confirming the results reported in [89]. The association of aluminum-containing vaccines in general with autism does not quite make statistical significance ($p = 0.06$) compared to non-aluminum-containing vaccines. We explain this observation through the high fever associated with MMR, a non-aluminum-containing vaccine, that leads to the common practice of administering acetaminophen [25], which the autistic child cannot adequately detoxify. However, the fact that autism is so clearly associated with Hep-B gives one pause.

4.5. Limitations of the VAERS Database and the Experiments

Cases of vaccine injury are most likely vastly underreported by physicians to VAERS, as has been observed for physician reports of drug adverse reactions [115]. We identified only 1,734 mentions of autism in the entire dataset, whereas the National Vaccine Injury Compensation Program, established in 1988, reports over 5,000 claims that autism is associated with vaccines. Another limitation is that it is not easy to distinguish cases where autism may have been a preexisting condition affecting the child's sensitivity to the vaccine, as contrasted with cases where the vaccine may have preceded, and therefore may potentially be causative in, a later diagnosis of autism. Finally, both patients and physicians can submit reports, so quality control due to reporting bias or lack of expertise may be an issue. Not all of the reports contain a record of the date of the vaccination, and this introduces some error in the temporal relationships.

5. Discussion

Autism is a disorder affecting cognitive and social skills that has severe implications on the ability of the affected individual to lead a productive and independent life. The alarming increase in the incidence of ASD in the last decade suggests that, while genetic factors are contributory, environmental triggers must also play a decisive role. In this paper, we argue that ASD is a condition characterized by a serum deficiency in sulfur metabolites, particularly the sulfate anion, which results in an inability to safely dispose of mercury, aluminum, and acetaminophen.

While the autism community has focused on the mercury in thimerosal as the main culprit in vaccines, our studies with the VAERS database have identified aluminum and acetaminophen as being likely even more damaging than mercury. Aluminum binds strongly to sulfur-containing molecules, and the body depends on sulfur for the proper elimination of both aluminum and acetaminophen, as well as mercury. Because of the sulfur deficiencies, aluminum, mercury and acetaminophen likely accumulate in the autistic brain, leading to further damage.

In [116], it is argued that safety assessments for vaccines have not included appropriate toxicity studies because vaccines have not been viewed as inherently toxic, but that this point of view should be revisited in light of the increased awareness of the potential toxicity of aluminum, particularly for infants and young children. They argue further that it is now well established that a bidirectional neuro-immune cross-talk regulates both the immune system and brain function.

The incidence of autism-related adverse events in the VAERS database continued to rise over the time period after the amount of thimerosal in the vaccines had been sharply reduced. We hypothesize that this unanticipated consequence is due to simultaneous increases in the aluminum content, attributed to an increased number of required vaccines, intentional addition of aluminum to achieve an adjuvant effect, as well as the likely further accumulation of aluminum as a consequence of leaching, given the new practice of storage in individual glass vials with rubber stoppers. We identified several severe adverse reactions that were much more prevalent in reports from the second decade of the data, and showed that these same symptoms were also much more prevalent for reports involving aluminum-containing vaccines compared to reports on vaccines without aluminum, over the entire data set. These symptoms include seizure, cyanosis, gaze palsy, depression, fatigue, insomnia, and death.

Possibly contradictory to our proposal is a study which showed elevations of lead, mercury and uranium in hair analyses of 40 children with autism compared with 40 controls, but these authors found no elevation of aluminum in the hair [117]. However, the result on mercury contradicts another study which showed reduced mercury in the hair of infants with autism [118], and a third study which showed no statistical difference in mercury content of hair between children with autism and controls [119]. A study in rats showed that oral antibiotics dramatically inhibit mercury excretion to 10% of normal levels [120]. It is conceivable that an inability to export aluminum into the hair, due to severe sulfate depletion, could complicate the interpretation of a metric based on aluminum content in hair.

The depleted supply of sulfate in the blood stream leads to increased vulnerability to vascular stress, in turn leading to excess immune cell activation, inflammation, permeability leaks, and blood clots, attributable mainly to a low ZP. This same deficiency interferes with the child's ability to dispose of the aluminum, which eventually accumulates in the brain and interferes with neural transmission. It is also likely that further aluminum exposure comes from aluminum in skin products such as high SPF sunscreen, particularly for the child whose barrier function is defective due to inadequate cholesterol sulfate and filaggrin in the epidermis. Other potential sources of aluminum are aluminum flocking agents in municipal water supplies, aluminum leaching from aluminum baby formula cans, and aluminum in the human milk supply to the breastfeeding infant, absorbed by the mother from sunscreen, antiperspirants, antacid medications, cooking utensils, *etc*.

Our specific studies on the MMR vaccine and the Hep-B vaccine further support our theories involving aluminum and acetaminophen toxicity. In an analysis of the distribution of vaccine types in events associated with autism versus the controls, we determined that MMR was highly over-represented in the cases associated with autism. A possible explanation is that the high fever associated with a reaction to MMR led to the administration of acetaminophen, whose safe disposal, like that of aluminum, depends on an adequate serum supply of bio-sulfates. The frequent presence of concurrent aluminum-containing vaccines would contribute synergistically to toxicity.

We hypothesize that the fever associated with MMR results in the administration of acetaminophen, which, in conjunction with the intense immune response to live viruses, becomes toxic to the vulnerable child. Most of the symptoms associated with Hep-B administration to children under 6 years old are also associated with aluminum-containing vaccines in general and over all age groups, further bolstering the hypothesis that the aluminum in the vaccine is a major source of toxicity. A strong association between Hep-B and autism also suggests that aluminum may contribute to autism.

This strong association does not however exclude mercury as a contributor to autism, given that Hep B has both mercury and aluminum. In fact, mercury and aluminum together may be synergistically toxic [113].

If our hypothesis is correct, then it should be relatively easy and very cost-effective to implement a solution to the problem. Both women of childbearing age and children should be encouraged to consume foods that are rich in sulfur and to spend considerable time outdoors without sunscreen on sunny days. It might be prudent to implement a screening test for sulfate and/or glutathione concentration in the blood prior to administration of an aluminum-containing vaccine, and to waive the vaccine or consider a non-aluminum-containing alternative if sulfate or glutathione levels are insufficient. A delay by one month of the current practice of Hep-B administration *at birth* seems warranted. The practice of including aluminum in the so-called "placebo" in vaccine trials should be abolished, so that the effects of aluminum adjuvant can be formally measured in a premarket phase. It would also be highly recommended to reconsider whether the increased immune response associated with aluminum adjuvant is worth the price in terms of increased risk of adverse reactions. Based upon our statistical research of the VAERS database, we would encourage the vaccine industry to consider omitting aluminum adjuvant doping of all vaccines for both children and adults.

In future work, we plan to create and maintain a web site where users can intelligently search the VAERS database, asking questions in spoken or typed natural language, such as, "Is there an association between miscarriage and the Gardasil vaccine?" An intuitive graphical interface will also help users easily find adverse event reports relevant to their personal experiences. This system will be modeled after a similar system we have already constructed for prescription drugs [121]. We believe that the VAERS database is a rich resource, many of whose secrets are yet to be revealed.

6. Conclusion

In this paper, we have presented some analyses of the VAERS database which strongly suggest that the aluminum in vaccines is toxic to vulnerable children. While we have not shown that aluminum is directly causative in autism, the compelling evidence available from the literature on the toxicity of aluminum, combined with the evidence we present for severe adverse reactions occurring much more frequently following administration of aluminum-containing vaccines as compared to non-aluminum-containing vaccines, suggests that neuronal damage due to aluminum penetration into the nervous system may be a significant factor in autism. The fact that mentions of autism rose steadily concomitant with significant increases in the aluminum burden in vaccines, is highly suggestive. However, it is possible that other factors, such as more aggressive reporting or simultaneous increases in other environmental toxins, e.g., herbicides or pesticides, or aluminum in other products such as antiperspirants and antacids, may have contributed to these observed increases. We also observed a strong correlation between the MMR vaccine and autism, which we suggest could be explained by the effects of acetaminophen.

We have proposed elsewhere that an impairment in cholesterol sulfate synthesis in the skin and in the vasculature may be causative in autism, and we argue here that vaccines can act synergistically with this impairment in the vulnerable child. We propose that simple corrective measures such as increased sunlight exposure and decreased use of sunscreen may help protect a child from a severe

reaction to aluminum-containing vaccines, but we also feel that the vaccine industry should find a way to reduce or even eliminate the aluminum content in vaccines.

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