Exhibit G

AUTISM & ALUMINUM ADJUVANTS IN VACCINES

How Aluminum Adjuvants in Vaccines Can Cause Autism

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The Centers for Disease Control (CDC) asserts that vaccines and vaccine ingredients have been disproven as potential causes of autism. Statements by the CDC are generic and encompass all vaccines and vaccine ingredients. For example, the CDC states:

> *"Vaccines Do Not Cause Autism" "There is no link between vaccines and autism." "...no links have been found between any vaccine ingredients and autism spectrum disorder." (CDC website, August 2017)*

These statements are not supported by available science. The CDC's evidence supporting these statements is limited to the MMR vaccine (Taylor 2014), thimerosal preservative (Taylor 2014) and vaccine antigen exposure (DeStefano 2013).

Dr. Frank DeStefano of the CDC's Immunization Safety Office is co-author of a paper (Glanz 2015) which states:

> *"To date, there have been no population-based studies specifically designed to evaluate associations between clinically meaningful outcomes and non-antigen ingredients, other than thimerosal."*

This statement applies to, among other vaccine ingredients, aluminum adjuvant. Studies of MMR vaccine cannot be used as evidence of safety for other vaccines, for example vaccines that contain aluminum adjuvant. The overly-broad, generic assertions that no vaccines and no ingredients cause autism are thus not supported by scientific evidence. In fact, the CDC statements are contradicted by a large, consistent and growing body of scientific evidence, including:

1) studies showing neurotoxic and neuroinflammatory effects (e.g. microglial activation) from dosages of aluminum adjuvants lower than or approximately equal to dosages received by infants according to the CDC vaccine schedule (Crepeaux 2017, Petrik 2007, Shaw 2013, Shaw 2009);

2) studies linking vaccines to immune activation brain injury (Zerbo 2016, Li 2015);

3) studies showing that early-life immune activation is a causal factor in autism and other neurodevelopmental disorders and mental illnesses (e.g. schizophrenia) (Meyer 2009, Deverman 2009, Estes 2016, Kneusel 2014, Careaga 2017, Meyer 2014).

The accumulating evidence indicates that vaccine-induced immune activation, and aluminum adjuvants in particular, may cause mental illnesses and neurodevelopmental disorders, including autism.

In this paper, we present scientific evidence that aluminum adjuvants can cause autism and other brain injuries. Also, we explain why the studies allegedly supporting the safety of aluminum adjuvants do not show safety for adverse neurological outcomes.

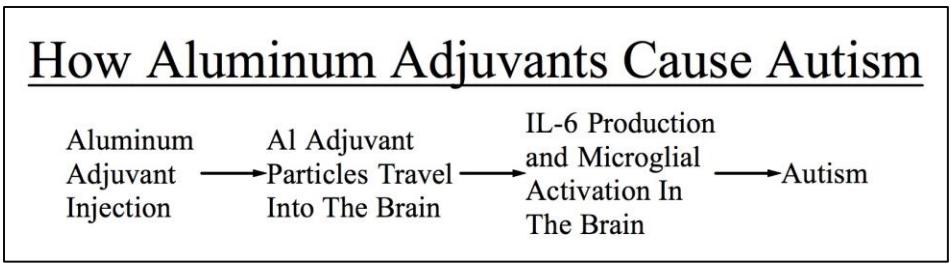

Fig 1: Proposed mechanism for how aluminum adjuvants cause autism. Each step is supported by replicated scientific studies.

Immune Activation: A Cause of Autism and Mental Illness

The term "immune activation" describes the activation of the cellular components of the immune system. The developing brain can be injured by immune activation, with life-long consequences (Meyer 2009, Deverman 2009, Estes 2016, Kneusel 2014, Careaga 2017, Meyer 2014). Immune activation injury is linked to autism, schizophrenia, depression and other mental illnesses or neurodevelopmental disorders. Immune activation effects on the brain are mediated by immune system signaling molecules, especially cytokines (Estes 2016, Meyer 2014, Smith 2007, Choi 2016, Pineda 2013).

It is generally accepted that immune activation (e.g., from infection) during pregnancy is a risk factor for autism and schizophrenia in the offspring (Ciaranello 1995, Atladottir 2010, Brown 2012). The intensity and duration of immune activation and cytokine expression appear to be important factors influencing autism risk (Meyer 2014). Intense immune activation is associated with greater risk of autism (Careaga 2017, Atladottir 2010). Chronic inflammation is associated with greater risk of autism (Jones 2016, Zerbo 2014). However, there is no evidence that short-duration, low-intensity immune activation resulting from common childhood illnesses increase autism risk. Timing of immune activation in relation to stages of brain development is also an important factor (Meyer 2006, Meyer 2009).

Animal experiments have tested the effects of immune activation during pregnancy and postnatally on the development of offspring (Meyer 2009, Deverman 2009, Estes 2016, Kneusel 2014, Careaga 2017, Meyer 2014). In these experiments, pregnant animals (mice, rats and monkeys) or neonates are injected with a non-infectious immune activating substance such as "poly-IC" (which mimics a viral infection) or lipopolysaccharide (LPS, which mimics a bacterial infection). These substances cause immune system activation without infection. They induce fever and cytokine production and can have substantial effects on brain development if activation is sufficiently intense or prolonged and if exposure occurs during vulnerable developmental stages.

Immune activation has been demonstrated in mice to cause the three core behavioral symptoms of autism: decreased socialization and communication, and increased repetitive behaviors (Malkova 2012). Immune activation has also been shown to cause neuropathology (Weir 2015) and behavioral abnormalities in monkeys that resemble behaviors in human schizophrenia and autism (Bauman 2014, Machado 2015). See Fig. 2.

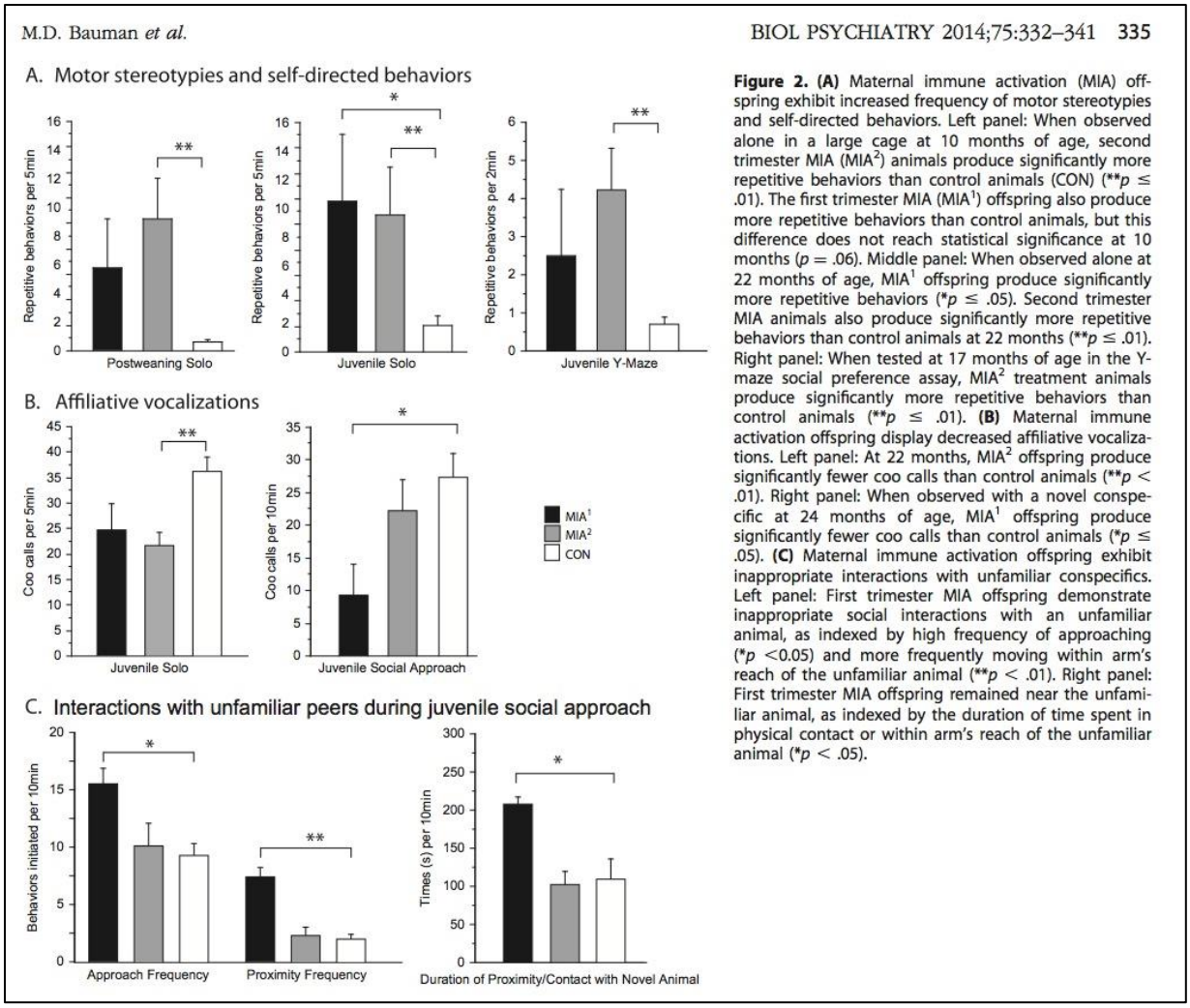

Figure 2. (A) Maternal immune activation (MIA) offspring exhibit increased frequency of motor stereotypies and self-directed behaviors. Left panel: When observed alone in a large cage at 10 months of age, second trimester MIA (MIA^2) animals produce significantly more repetitive behaviors than control animals (CON) (**$p \leq .01$). The first trimester MIA (MIA^1) offspring also produce more repetitive behaviors than control animals, but this difference does not reach statistical significance at 10 months ($p = .06$). Middle panel: When observed alone at 22 months of age, MIA^1 offspring produce significantly more repetitive behaviors (*$p \leq .05$). Second trimester MIA animals also produce significantly more repetitive behaviors than control animals at 22 months (**$p \leq .01$). Right panel: When tested at 17 months of age in the Y-maze social preference assay, MIA^2 treatment animals produce significantly more repetitive behaviors than control animals (**$p \leq .01$). **(B)** Maternal immune activation offspring display decreased affiliative vocalizations. Left panel: At 22 months, MIA^2 offspring produce significantly fewer coo calls than control animals (**$p < .01$). Right panel: When observed with a novel conspecific at 24 months of age, MIA^1 offspring produce significantly fewer coo calls than control animals (*$p \leq .05$). **(C)** Maternal immune activation offspring exhibit inappropriate interactions with unfamiliar conspecifics. Left panel: First trimester MIA offspring demonstrate inappropriate social interactions with an unfamiliar animal, as indexed by high frequency of approaching (*$p < 0.05$) and more frequently moving within arm's reach of the unfamiliar animal (**$p < .01$). Right panel: First trimester MIA offspring remained near the unfamiliar animal, as indexed by the duration of time spent in physical contact or within arm's reach of the unfamiliar animal (*$p < .05$).

Fig 2: Maternal immune activation in monkeys caused behavioral abnormalities in juvenile offspring resembling behaviors in both autism and schizophrenia. MIA1 (Black)= first trimester immune activation; MIA2 (grey) 2nd trimester immune activation; CON (white) saline control. From Bauman et al. 2014

Immune activation also causes non-behavioral effects associated with human autism (citations here link immune activation with these effects):

1) reduction in Purkinje cells (Shi 2009);
2) mitochondrial dysfunction (Giulivi 2013);
3) increase in brain volume (from IL-6 exposure, Wei 2012(b)) and neuron density in the brain (Smith 2012);
4) long term chronic brain inflammation (Garay 2012); and
5) microbiome disruption (dysbiosis) (Hsiao 2013).

These non-behavioral similarities further support the relevance of the immune activation models to human autism. The non-behavioral (e.g., physiological) effects of immune activation have been reviewed (Labouesse 2015).

The cytokines interleukin-6 (IL-6) and interleukin-17a (IL-17) have been identified as mediating the behavioral effects of immune activation (Smith 2007, Malkova 2012, Choi 2016, Pineda 2013, Wei 2012(a), Wei 2013, Parker-Athill 2010, Wei 2016). The IL-6 findings have been replicated by different researchers using a variety of experimental methods. For example, in an experiment with

poly-IC, abnormal behavior is almost completely prevented by simultaneous administration of IL-6-blocking antibody (Smith 2007, Pineda 2013). Injection of IL-6 by itself causes abnormal behavior that closely matches behavior resulting from poly-IC immune activation (Smith 2007). Inhibition of IL-6 signaling in a genetic autism model (BTBR mice) normalized social and repetitive behavior (Wei 2016). These results demonstrate that IL-6 is responsible for causing abnormal autism-like behavior.

The Patterson laboratory at CalTech was the first to report that IL-6 is responsible for causing the autism-like behavioral effects of immune activation (Smith 2007). Two papers from this research group state:

> *"IL-6 is central to the process by which maternal immune activation causes long-term behavioral alterations in the offspring." (Smith 2007)*

> *"…blocking IL-6 prevents >90% of the changes seen in offspring of poly(I:C)-injected females, showing that gene expression changes, as well as behavioral changes, are normalized by eliminating IL-6 from the maternal immune response." (Smith 2007)*

> *"IL-6 is necessary and sufficient to mediate these effects since the effects…are prevented by injection of pregnant mice with poly-IC combined with an anti-IL-6 antibody, and are mimicked by a single maternal injection of IL-6." (Garay 2013)*

Brain exposure to elevated IL-6 by engineered virus showed that IL-6 exposure, initiated after birth, caused autism-like behaviors (Wei 2012(a)). The Wei 2012(a) paper states:

> *"We demonstrated that IL-6 is an important mediator of autism-like behaviors. Mice with an elevated IL-6 in brain developed autism-like behaviors, including impaired cognition ability, deficits in learning, abnormal anxiety-like trait and habituation, as well as a decreased social interaction initiated at later stages. These findings suggest that an IL-6 elevation in the brain could modulate certain pathological alterations and contribute to the development of autism." (Wei 2012(a))*

More recent evidence shows that IL-17 acts downstream of IL-6 to cause autism-like behavioral abnormalities and atypical cortical development in mice (Choi 2016). Blocking either IL-6 or IL-17 prevents the autism-like behavior; an injection of IL-17 by itself causes the autism-like behavior (Choi 2016). IL-6 is known to induce IL-17 by promoting the development of Th17 cells which produce IL-17.

Immune activation animal models appear to be valid models for human neurological/psychiatric disorders, including autism (Estes 2016, Careaga 2017, Meyer 2014). The Estes 2016 review argues for the validity of the immune activation models to humans:

> *"These MIA (maternal immune activation) animal models meet all of the criteria required for validity for a disease model: They mimic a known disease-related risk factor (construct validity), they exhibit a wide range of disease-related symptoms (face validity), and they can be used to predict the efficacy of treatments (predictive validity)." (Estes 2016)*

Evidence suggests a mediating role for IL-6 and IL-17 in human autism. For example, IL-6 is significantly elevated in the cerebellum in human autism (Wei 2011) and is highly elevated in some brain regions of some autistic individuals (Vargas 2005). Treatment of human autistics with the anti-inflammatory flavonoid luteolin improves autistic behaviors in the individuals that also experience a decline in IL-6 blood levels (Tsilioni 2015). This result is consistent with a causal role for IL-6 in human autism. Also, IL-17 is elevated in human autism (Akintunde 2015, Al-Ayadhi

2012, Suzuki 2011). Vitamin D reduces IL-17 production (Bruce 2011, Wobke 2014, Drozdenko 2014) and improves autistic behaviors in humans (Saad 2016, Jia 2015). The vitamin D findings are consistent with a causal role for IL-17 in human autism.

IL-6 functioning appears to be similar or identical in mice and humans. No mouse-human differences in IL-6 functioning are described in a 2004 review (Mestas 2004). IL-6 functioning is quite conserved across species (Brown 2014). Central nervous system development in rodents and humans is governed by the same principles (Brown 2014). Hence, the fact that IL-6 causes autism-like behavioral abnormalities in animal models deserves a presumption of validity to humans.

Immune activation is a risk factor for autism, schizophrenia and other neurological/psychiatric disorders. The cytokines IL-6 and IL-17 are responsible for mediating the autism-like behavioral effects of immune activation in the animal models. The available evidence supports a causal role for IL-6 and IL-17 in human autism.

Maternal vs. Postnatal Immune Activation

The timing of immune activation is an important factor influencing effects on the brain. The developing brain is vulnerable to immune activation injury; the mature, adult brain is apparently not nearly as vulnerable. Sensitivity to immune activation likely declines as the brain matures (Meyer 2014, Meyer 2007).

In most immune activation experiments, the offspring are exposed to immune activation during gestation (by stimulating the maternal immune system). In contrast, most vaccines are administered postnatally. This raises the question of whether postnatal immune activation can have similar effects on the brain as maternal immune activation. Diverse evidence indicates that the brain can be adversely affected by postnatal immune activation. Postnatal immune activation experiments, human case reports, and consideration of brain development timelines suggest that the human brain is vulnerable to immune activation injury for years after birth.

In the maternal immune activation experiments, inflammatory signaling and some cytokines (e.g. IL-6) traverse the placenta into the fetus. Consequently, immune activation in the mother causes immune activation and elevated cytokines in the fetus, and in the fetal brain (Oskvig 2012, Ghiani 2011).

Postnatal immune activation can have adverse neurological effects, including increased seizure susceptibility (Chen 2013, Galic 2008), learning and memory deficits (Harre 2008), and an increase in excitatory synapse formation (Shen 2016). Seizure disorders, learning and memory dysfunction, and elevated excitatory signaling are associated with autism.

Elevated IL-6 in the brain in the postnatal period causes neuronal circuitry imbalance and mediates autism-like behaviors in mice (Wei 2012(a)). The circuitry imbalance observed in Wei 2012(a) was an excess of excitatory synapses and a deficit of inhibitory synapses. See Fig. 3. Excessive excitatory signaling is observed in human autism (Robertson 2016, Freyberg 2015). In fact, an imbalance between excitatory and inhibitory signaling (towards excess excitation) has been posited as a central characteristic of autism (Robertson 2016, Freyberg 2015).

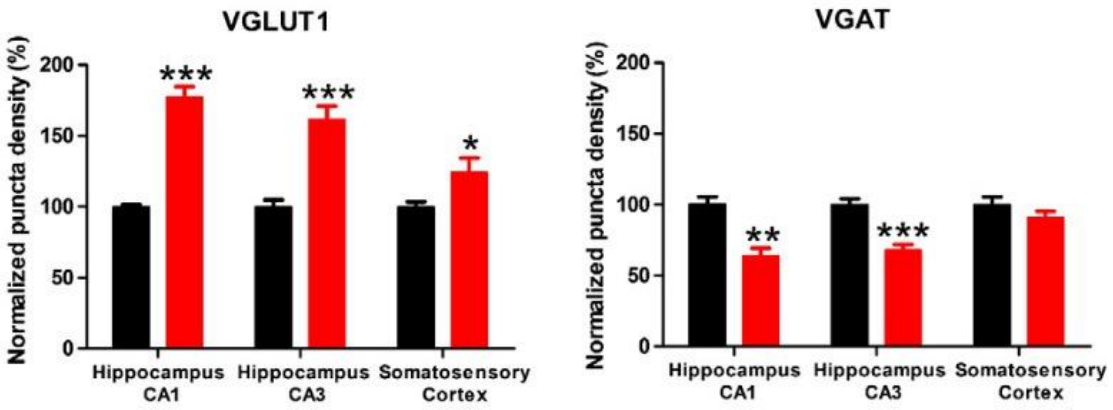

Fig 3: Elevation of IL-6 in the brains of mice (initiated shortly after birth) caused an increase in excitatory synapses (VGLUT1) and a decrease in inhibitory synapses (VGAT). Excessive excitatory signaling is observed in human autism. Red=Elevated IL-6; Black=Control. VGLUT1=excitatory synapses; VGAT=inhibitory synapses. *P<0.05, **P<0.01 and ***P <0.001. Adapted from Wei et al 2012(a).

In a maternal immune activation experiment with mice (Coiro 2015), autism-relevant behavior and dendritic spine abnormalities (relevant to autism and schizophrenia) were ameliorated by administering an anti-inflammatory drug postnatally. The drug was started at birth and continued for 2 weeks, which roughly corresponds to age 2 in humans (Semple 2013). This result indicates that brain development is affected by postnatal inflammation, at times corresponding to when vaccines are given to humans.

Several case reports describe previously-healthy children that displayed sudden-onset autistic behavior during or subsequent to infection in the brain. All the cases had signs of intense brain inflammation. Here are brief descriptions:

Delong 1981: describes 3 children, ages 5, 7 and 11 with full-blown autistic behavior associated with brain inflammation. Brain inflammation was presumed in two cases and confirmed in one. The 5 and 7 year olds recovered completely, and the 11-year recovered partially.

Marques 2014: describes a previously healthy 32-month-old girl that suffered autistic regression from a viral central nervous system infection with associated brain inflammation.

Ghaziuddin 2002: describes a previously healthy 11-year-old boy that suffered permanent autistic regression after sudden onset herpes brain infection with associated brain inflammation.

Gillberg 1986: describes a previously healthy 14-year-old girl with permanent autistic regression from herpes brain infection with associated brain inflammation.

The most parsimonious explanation for these cases is that autistic behavior resulted from intense inflammation and cytokine production in the brain. Accordingly, these cases indicate that the human brain remains vulnerable to immune activation injury well into childhood, though the vulnerability almost certainly decreases with maturation. The susceptibility of older children to inflammation-induced autistic behavior strongly suggests that younger infants, of 0-2 years of age, are also vulnerable. It is not reasonable to claim, and there is no evidence to suggest, that the age range of 0-2 years (when most vaccines are given) is uniquely resistant to immune activation

injury. All the available evidence indicates the opposite.

The immune activation experiments and case reports are consistent and indicate that immune activation and elevated cytokines in the postnatal period can cause brain injury.

The next critical question to consider is whether vaccines can cause immune activation and elevated cytokines in the brain.

Postnatal Vaccination Affects Brain Development in Animal Model

The first study to test the effect of postnatal vaccination on brain development was published in 2015 (Li 2015). In this experiment, neonatal rats were administered bacillus calmette-guerin (BCG) vaccine, hepatitis B (HBV) vaccine or a combination (BCG+HBV) timed to imitate human infant vaccination schedules. BCG and HBV vaccines produced opposite effects on the brain. Specifically, BCG enhanced synaptic plasticity and long-term potentiation (LTP, the basis for learning and memory); HBV inhibited synaptic plasticity and LTP. BCG and HBV vaccines also caused opposite changes in some synapse protein levels.

HBV vaccine (but not BCG vaccine) increased IL-6 gene expression in the brain; increased gene expression likely indicates an elevation in brain IL-6. The HBV vaccine contains aluminum adjuvant, and the BCG does not contain aluminum adjuvant. Hence, the aluminum adjuvant may be the ingredient responsible for the elevated IL-6 gene expression. See Fig. 4.

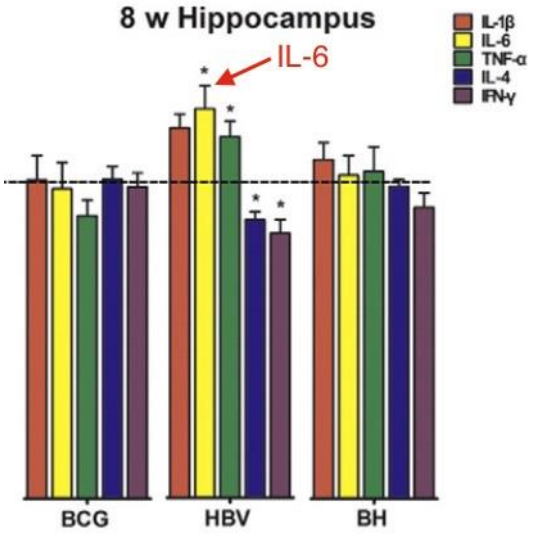

Fig. 4: Hepatitis B vaccine, but not BCG vaccine, increased IL-6 gene expression in the brain at 8 weeks after neonatal vaccination. Hepatitis B vaccine contains aluminum adjuvant; BCG vaccine does not. Elevated IL-6 causes autism-like behaviors in animal models. *P<0.05 Adapted from Li et al 2015.

The Li et al study showed that the vaccines caused other changes in the brain, including 1) changes in long-term potentiation (LTP) (Hep B decreased LTP), 2) changes in dendritic spines, and 3) changes in synapse protein expression. Changes in synapse proteins and dendritic spines have been observed in human brain disorders.

Li et al. attribute the brain effects to changes in cytokine levels and immune polarization (Th1/Th2 polarization) induced by the vaccines. Aluminum adjuvants cause

Th2 polarization. Li et al. state that the results suggest vaccines can interact by way of immune activation effects:

> *"…our data suggested that combinations of different vaccines can mutually interact (enhance or counteract). The mechanism of synaptic plasticity modulation through neonatal BCG/HBV vaccination may be via systemic Th1/Th2 bias accompanied by a specific profile of cytokines and neurotrophins in the brain." (Li 2015)*

Li 2015 demonstrates that vaccines affect brain development by an immune activation mechanism. Further, since aluminum adjuvants induce Th2 activation and long term Th2 polarization, the Li 2015 results suggest that all aluminum-adjuvanted vaccines may cause adverse effects similar to the HBV vaccine. Accordingly, the Li 2015 results suggest that studies showing that immune activation causes neurological/psychiatric disorders are relevant to vaccine adverse effects.

Vaccines Are Given During Synaptogenesis

Another way to answer the question of brain vulnerability to immune activation is to consider the types of brain development processes occurring when vaccines are administered. Vaccines are given primarily in the first 18 months after birth. The human brain undergoes intense and rapid development during this period. Synaptogenesis (formation of synapse connections between neurons) is especially intense in this period.

The vulnerability of the developing brain to immune activation is apparently related to the specific types of brain development processes occurring (Tau 2010, Meyer 2006, Meyer 2007). Such processes include migration (movement of neurons to final locations in the brain), adhesion (formation of chemical-mechanical attachments between brain cells), and synaptogenesis (formation of synapse connections between neurons), among others (neurogenesis, gliogenesis, myelination etc).

Cytokines affect brain development processes. For example, elevated IL-6 affects migration, adhesion and synaptogenesis (Wei 2011). Elevated IL-6 in the postnatal period promotes an excess of excitatory synapses and a deficit of inhibitory synapses, and mediates autism-like behaviors (Wei 2012(a)).

In humans, a dramatic increase in synaptogenesis begins around the time of birth, and continues until about age 3 (Huttenlocher 1997, Tau 2010, Stiles 2010, Semple 2013). Vaccines are administered during this intense synaptogenesis. See Figs. 5-6. Elevated brain IL-6 induced by vaccination during synaptogenesis may cause an excitatory-inhibitory imbalance, towards excitation. An excitatory imbalance has been observed in human autism (Robertson 2016, Freyberg 2015).

Synaptogenesis tapers off through childhood and adolescence. This fact may explain why some older children and teens can suffer autistic regression after intense brain inflammation, but apparently become less vulnerable to immune activation brain injury with age.

Intense synaptogenesis occurs at ages 0-18 months, when many vaccines are administered. Consequently, vaccines may adversely impact synaptogenesis if they induce inflammation or IL-6 in the brain.

The timing of brain development processes in humans supports the idea that the human brain is vulnerable to immune activation and cytokines in the first few years after birth, when vaccines are administered. Disruption of synaptogenesis by vaccine-induced immune activation is a particular concern.

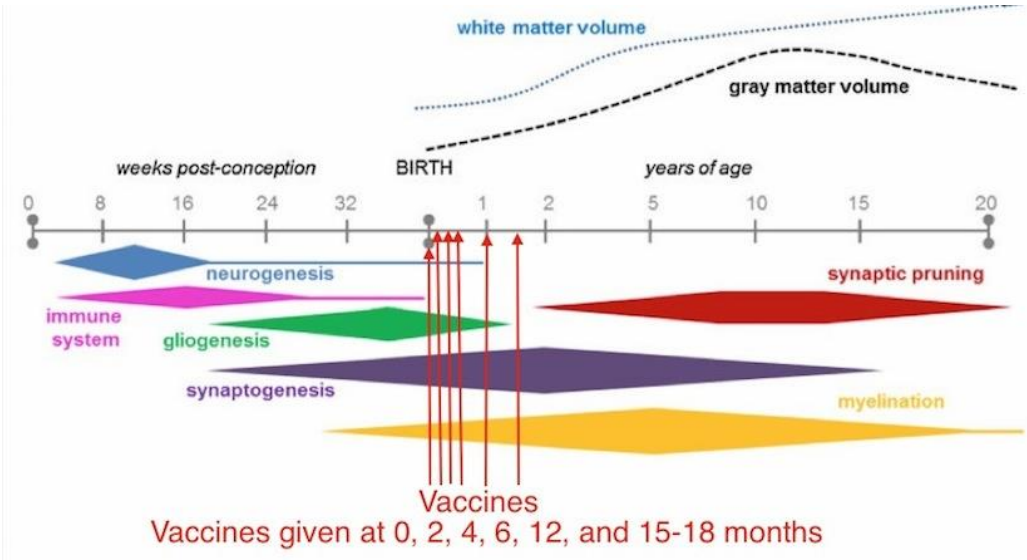

Fig. 5: Timeline of specific brain developmental processes in humans. Synaptogenesis is most intense during the first couple years of life, when vaccines are administered. Timing of vaccination according to the CDC vaccine schedule is shown. Elevated IL-6 during synaptogenesis may cause an excitatory-inhibitory synapse imbalance, towards excitation. Adapted from Semple 2013.

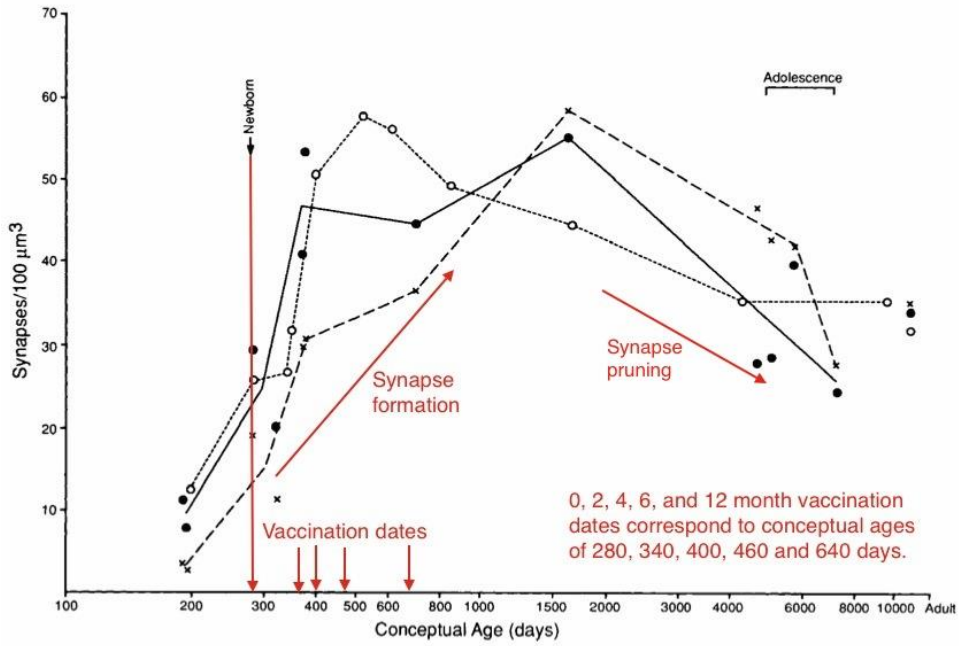

Fig. 2. Mean synaptic density in synapses/100 µm^3 in auditory, calcarine, and prefrontal cortex at various ages. Open circles, visual cortex (area 17); filled circles, auditory cortex; x, prefrontal cortex (middle frontal gyrus).

Fig. 6: Measurements of synapse density in human cadavers of various ages indicate a dramatic increase in synapses in the first few years of life. Vaccines are administered during intense synapse formation. Elevated IL-6 during synaptogenesis may cause an excitatory-inhibitory synapse imbalance, towards excitation. Image adapted from Huttenlocher and Dabholkar 1997.

Aluminum Adjuvants: Neurotoxic At Vaccine Dosages

Aluminum (Al) adjuvants have an essential role in many vaccines: to stimulate immune activation. Without Al adjuvants, these vaccines would have greatly reduced efficacy.

Aluminum adjuvants comprise sub-micron particles (primary particles) of aluminum compounds, typically AlOH, AlPO4, AlSO4 or mixtures. The primary particles are typically agglomerated into larger particles with sizes of about 2-20 microns (Harris 2012). The Al adjuvant materials have low solubility in water and body fluids. Al adjuvant particles are biopersistent and can remain in the body for months or years (Flarend 1997, Khan 2013, Gherardi 2001).

Aluminum ingested in the diet has low oral absorption (about 0.3%), is rapidly excreted by the kidneys, is (mostly) excluded from the brain by the blood-brain barrier, and is in a solubilized, Al3+ ionic form (not particulate). These defenses are adequate for protecting the brain from natural levels of aluminum exposure. These protective mechanisms are unable to protect the brain from injected aluminum adjuvant particles. Al adjuvant particles are too large to be removed by the kidneys, and are carried across the blood-brain barrier by macrophages.

Dosages of aluminum adjuvants received by infants according to the CDC vaccination schedule are:

Birth (Hep B):
74 mcg/kg (250 mcg for 3.4 kg infant)

2 month:
245 mcg/kg (1225 mcg for 5 kg infant)

4 month:
150 mcg/kg (975 mcg for 6.5 kg infant)

6 month:
153 mcg/kg (1225 mcg for 8 kg infant)

These are maximum-possible dosages (because different vaccine products have different amounts) for average-weight infants.

Accumulating evidence shows that aluminum adjuvants have adverse neurological effects at dosages lower than or approximately equal to dosages infants receive from vaccines. These effects appear to depend on the particulate nature and biopersistence of the aluminum adjuvant. Injected Al adjuvant has adverse effects that are apparently mediated by the particles and independent of solubilized Al3+ ions released by the slowly dissolving particles (Crepeaux 2017).

Al adjuvant injections in mice cause adverse effects at vaccine-relevant dosages of 100, 200, 300 and 550 mcg/Kg body weight (Crepeaux 2017, Shaw 2009, Petrik 2007, Shaw 2013). These include deficits in learning and memory (Shaw 2009), deficits in neuromuscular strength/function (Petrik 2007), and changes in locomotor activity and/or gait (Shaw 2009, Shaw 2013). Autism is associated with gait and movement abnormalities (Kindregan 2015) and memory dysfunction (Williams 2006).

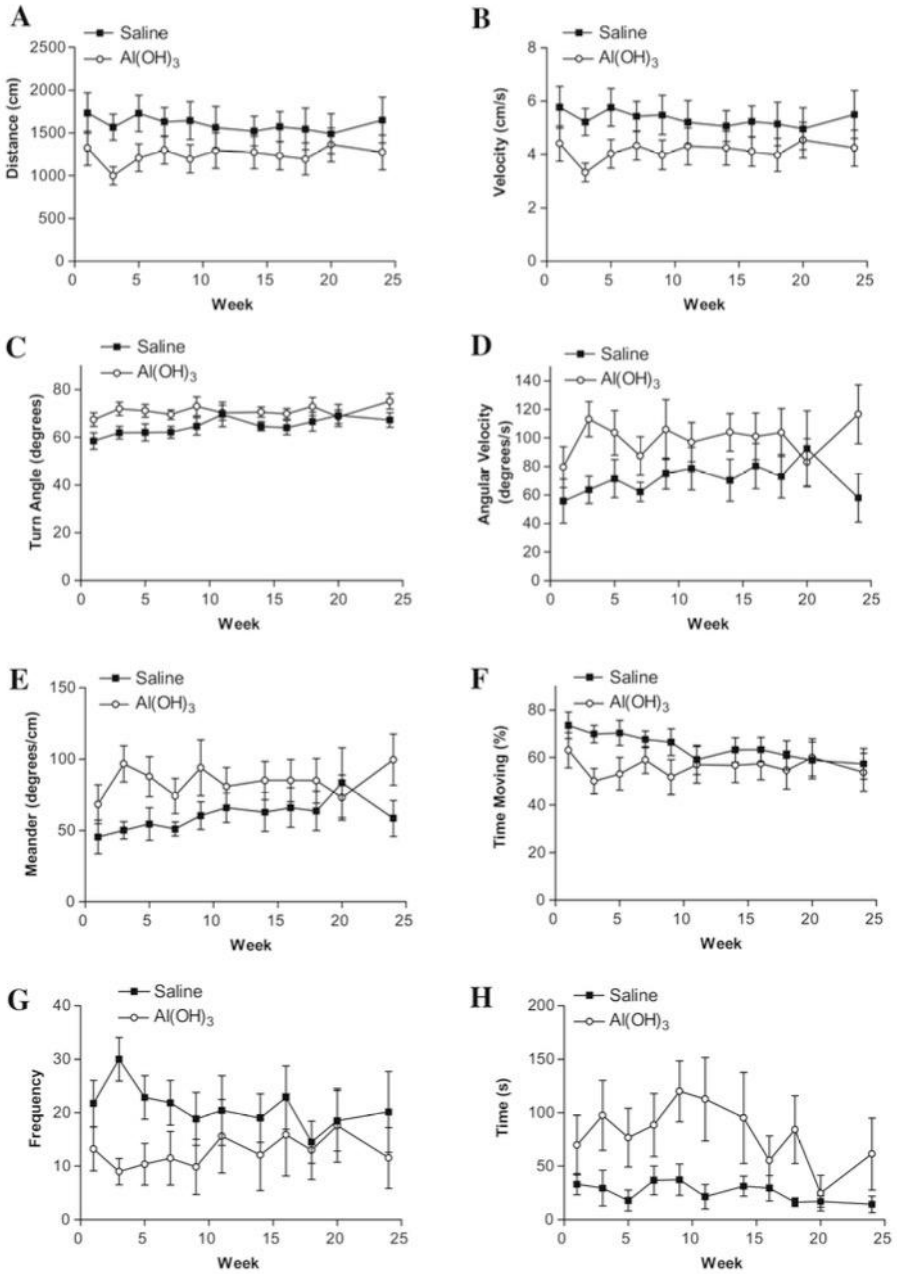

Fig. 4.
Open field movement analysis as an assessment of spontaneous activity and anxiety in control mice vs. mice injected six times with aluminum hydroxide. Aluminum hydroxide injected mice showed the following behavioural changes: (A) Shorter distances moved (***$p < 0.0001$). (B) Slower movement (***$p < 0.0001$). (C) Greater mean turn angle (***$p < 0.0001$). (D) More rapid turning (***$p < 0.0001$). (E) Greater meander (***$p < 0.0001$). (F) Smaller percentage of time in overall movement (**$p = 0.0030$). (G) Fewer entries into the centre of the open field (***$p < 0.001$). Late entry into centre (***$p < 0.0001$). (All measures, two-way ANOVA).

Fig. 7: Dosage of 300mcg/Kg AlOH adjuvant caused large and persistent changes in exploratory behavior and movement in open field tests. This is an indicator of neurotoxicity. Human autistics also display abnormal movement and exploratory behavior. Adapted from Shaw and Petrik 2009.

Al adjuvant dosages of 200mcg/Kg (as 3 x 66mcg/Kg) (Crepeaux 2017) and 300mcg/Kg (as 6 x 50mcg/Kg) (Shaw 2009) increased microglial activation in the ventral forebrain and lumbar spinal cord, respectively. The elevated microglial activation was measured about 6 months after Al adjuvant injection, which suggests that the microglial activation is chronic. Activated microglia indicate an ongoing inflammatory process and suggest the presence of elevated cytokines. Human autistics have activated microglia and elevated cytokines throughout the brain (Vargas 2005, Suzuki 2013, Li 2009).

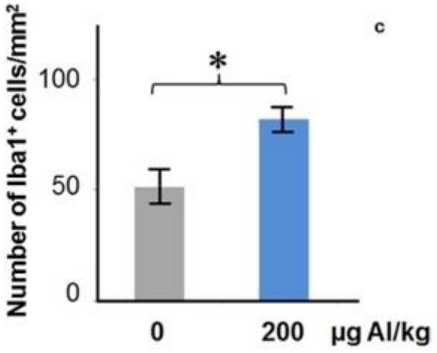

Fig. 8: Al adjuvant (200mcg/Kg) caused an increase in microglial activation in the brain of mice. The protein iba1 indicates activated microglia. Measurements were performed 6 months after Al adjuvant injection, indicating that the microglial activation is a chronic condition. * P<0.05. From Crepeaux et al., 2017.

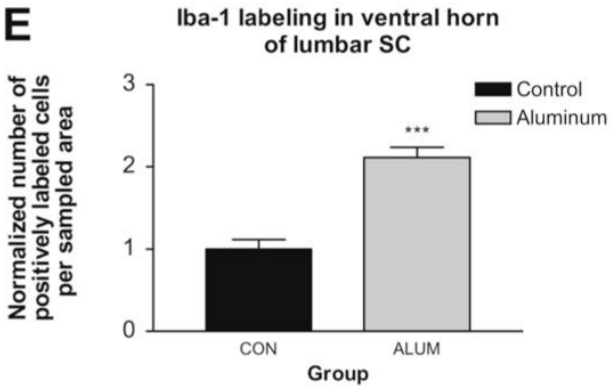

Fig. 9: Al adjuvant (300mcg/Kg) caused an increase in microglial activation in the lumbar spinal cord of mice. The protein iba1 indicates activated microglia. Measurements were performed 6 months after Al adjuvant injection, indicating that the microglial activation is a chronic condition. ****p* < 0.001, one-way ANOVA. From Shaw and Petrik 2009.

Activated microglia are implicated as a causal factor in autism, because microglia mediate inflammation in the brain. Microglia can produce IL-6 when in an activated state. A recent review on microglia and autism (Takano 2015) states:

> *"…any factors that alter the number or activation state of microglia either in utero or during the early postnatal period can profoundly affect neural development, thus resulting in neurodevelopmental disorders, including autism." (Takano 2015)*

Microglia appear to play an important role in the causation of autism (Takano 2015, Kneusel 2014). Hence, the microglial activation caused by aluminum adjuvants suggests a role in autism.

Several studies show that Al adjuvants increase brain aluminum content (Crepeaux 2017, Flarend 1997, Shaw 2009, Khan 2013, Crepeaux 2015). A dosage of 200 mcg/Kg Al adjuvant caused a 50-fold increase in brain aluminum content in mice, from 0.02 ug/g to 1.0 ug/g dry weight of brain (Crepeaux 2017). These measurements were performed 6 months after the final injection, indicating that the Al persists in the brain long-term (Crepeaux 2017). See Fig. 10. Al adjuvants have been found to accumulate in the brain of mice up to one year after injection (Khan 2013). Crepeaux 2015 demonstrated persistence and increasing accumulation of Al adjuvant particles up to 270 days in spleen and lymph nodes of mice. Increasing accumulation of Al in distant organs over time suggests that toxic effects may increase with time, and may be delayed by months or years after exposure.

The 400 and 800 mcg/Kg doses used in the Crepeaux 2017 study did not cause adverse effects or elevated brain aluminum. The authors attribute this surprising inverted dose-response relationship to granulomas induced by the higher dosages. Granulomas trap the Al adjuvant at the injection site, thereby preventing its transport into the brain and other sensitive tissues. Granulomas occur after about 1% of vaccinations (Bergfors 2014). This is cause for concern because it indicates that, for 99% of vaccinations, the Al adjuvant can be transported around the body. It is not confined to a granuloma. See Fig. 11.

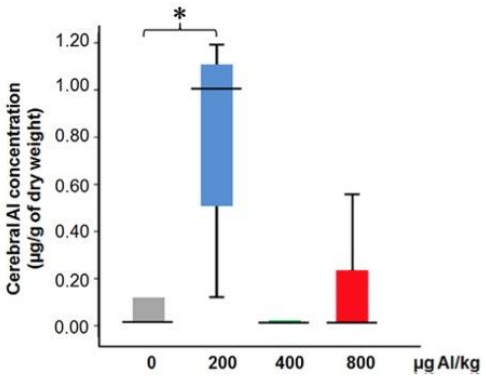

Fig. 10: Dosage of 200 mcg/Kg Al adjuvant caused a 50-fold increase in brain aluminum content, from 0.02 to 1.00 ug/g dry weight, in mice. Higher dosages (400 and 800 mcg/Kg) did not increase brain Al content, presumably because the higher dosages caused a granuloma at the injection site. A granuloma traps the Al adjuvant at the injection site, thereby preventing systemic dispersal and transport into the brain. These measurements were performed 6 months after the final injection, indicating that the Al persists in the brain long-term. *P<0.05. From Crepeaux et al., 2017.

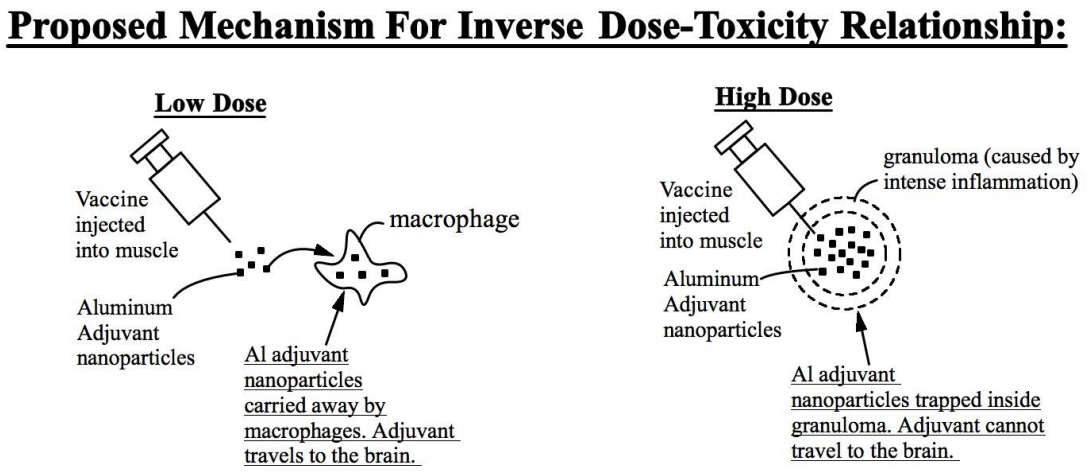

Fig. 11: High dose Al adjuvant injection into the muscle causes a granuloma, which traps the Al adjuvant and prevents it from traveling into the brain. Low dose does not form a granuloma. Hence, the lower dose is free to travel to the brain. Consequently, the lower dose is more toxic than the higher dose. This mechanism explains the surprising inverted dose-toxicity results of Crepeaux et al. 2017.

Particle Transport and Macrophage Chemotactic Protein (MCP-1)

Aluminum adjuvants travel into the brain (Khan 2013, Crepeaux 2015, Crepeaux 2017, Shaw 2009, Flarend 1997). Al adjuvant particles are carried through the blood-brain barrier and into the brain by macrophages (Khan 2013). Transport is promoted by macrophage chemotactic protein-1 (MCP-1) (Khan 2013). MCP-1 causes macrophages to travel around the body and into the brain. Particle transport into the brain by macrophages is well-established and has been investigated for therapeutic applications (Choi 2012, Pang 2016).

MCP-1 is elevated in the brains of human autistics (Vargas 2005) and is elevated in the blood of neonates later diagnosed with autism (Zerbo 2014). This suggests that neonates with high MCP-1 will experience elevated Al adjuvant transport into the brain when injected with Al adjuvanted vaccines. This is consistent with Al adjuvants causing autism by inducing immune activation and elevated cytokines in the brain.

Aluminum Induces IL-6 Expression In The Brain

Water-soluble aluminum salts (e.g. $AlCl_3$, Al lactate) induce elevated IL-6 in the brain and other tissues. In fact, aluminum appears to selectively induce IL-6 (Viezeliene 2013). Studies of aluminum exposure and IL-6 expression in the brain include:

Cao 2016: Ingestion of 30 or 90 mg/kg/day aluminum (as $AlCl_3$) for 90 days significantly increased gene expression of IL-6 and other cytokines in the brain (hippocampus).

Alawdi 2016: Ingestion of 3.4 mg/kg/day aluminum (as $AlCl_3$) for 6 weeks caused a 4-fold increase in IL-6 in the brain (hippocampus). This dosage is far lower than the outdated "no observed adverse effects level" (NOAEL) oral dosages (26 and 62 mg/kg/day) used as benchmarks for toxicity threshold (Mitkus 2011, Offit 2003).

In fact, other experiments show that oral dosages of 3.4, 4, 5.6, 6, and 20.2

mg/Kg/day aluminum cause numerous adverse effects in mice or rats and hence the NOAEL for orally ingested Al is currently unknown (Alawdi 2016, Dera 2016, Sethi 2008, Sethi 2009, Bilkei-Gorzo 1993).

The induction of IL-6 may occur because aluminum strongly induces oxidative stress (Exley 2003). Oxidative stress induces IL-6 expression (Viezeliene 2013).

CDC Website Cites Fatally Flawed Study Of Al Adjuvants (Mitkus 2011)

Dosages of Al adjuvants received by infants increased dramatically as the vaccine schedule was expanded in the 1980s and 1990s. However, as the vaccine schedule expanded, the increasing dosages of Al adjuvants were not tested for safety. Government agencies (HHS, NIH, CDC, FDA) have not pursued any new experimental work on Al adjuvant toxicity.

To support the safety of Al adjuvants at today's higher dosages, the CDC cites a 2011 FDA study of aluminum exposure from vaccines (Mitkus 2011). This study is the only scientific evidence cited by the CDC and FDA websites to support the safety of Al adjuvants.

The Mitkus 2011 study is a theoretical modeling study of Al adjuvant kinetics; it contains no new data concerning Al adjuvant toxicity (from animal models or epidemiology). Mitkus 2011 calculates a body burden of aluminum resulting from the slow dissolution of Al adjuvant particles, and compares the dissolved-aluminum body burden to a "minimal risk level" (MRL). The MRL is derived from a study of ingested Al toxicity in mice (Golub 2001). The Golub 2001 study provides the NOAEL (26 mg/kg/day ingested), which is converted into the MRL for human infants (based on 1mg/kg/day ingested) by using a safety factor of about 30.

The Mitkus study is fatally flawed for these reasons:

1) MITKUS ASSUMES AL ADJUVANT PARTICLES ARE HARMLESS

Mitkus makes an unstated assumption that Al adjuvants have zero toxicity while in particulate form. Mitkus only considers the potential toxicity of aluminum ions (Al3+) released by the slowly-dissolving Al adjuvant particles.

Al adjuvants comprise low-solubility and biologically-persistent microscopic particles. The Mitkus analysis assumes that the particles are absolutely nontoxic and perfectly harmless, even when present in the brain and other organs. Mitkus provides no justification for this unstated assumption. Further, the assumption is contradicted by recent findings on Al adjuvant toxicity (Crepeaux 2017) and particulate toxicity generally. Particles can have toxic effects mediated by surface chemistry (e.g. surface charge and surface catalytic activity) and particle shape, among other characteristics of solid particles (Sharifi 2012, Podila 2013).

Several studies show injected Al adjuvants cause behavioral abnormalities, abnormal weight gain, learning and memory impairment, motor neuron death/apoptosis, neuromuscular strength deficits, chronic microglial activation/brain inflammation, and large (e.g. 50X) increases in brain and spinal cord aluminum content (Petrik 2007, Shaw 2009, Shaw 2013, Crepeaux 2017). These adverse effects occur at dosages less than or approximately equal to dosages received by infants according to the CDC vaccine schedule.

2) NEW RESEARCH SHOWS INGESTED AL HARMFUL AT DOSAGES LOWER THAN 26 MG/KG/DAY

Mitkus assumes that Al adjuvant toxicity is mediated exclusively by solubilized Al (Al3+ ions) released by the slowly-dissolving Al adjuvant particles. To establish a threshold toxicity level from the solubilized Al, Mitkus relies on a mouse feeding study (Golub 2001) reporting a "no-observed adverse effects level" (NOAEL) oral dosage of 26 mg/Kg/day ingested aluminum. Mitkus

used a 30X safety factor for applying this dosage to humans, which is reasonable.

However, other experiments show that much lower oral dosages of 3.4, 4, 5.6, 6, and 20.2 mg/Kg/day aluminum cause adverse effects in mice or rats (Alawdi 2016, Dera 2016, Sethi 2008, Sethi 2009, Bilkei-Gorzo 1993). The adverse effects include chronic brain inflammation, learning and memory impairment, and kidney inflammation. So, the Mitkus analysis is wrong because 26 mg/kg/day is not a NOAEL. The "minimal risk level" (MRL) determined by Mitkus is too high by a factor of at least 26/3.4 = 7.6. Using a corrected NOAEL of 3.4 mg/Kg/day (based on Alawdi 2016) results in vaccine aluminum exposure exceeding the MRL for AlPO4 adjuvant, and approximately matching the MRL for AlOH adjuvant. The new, corrected MRL lines indicate that Al phosphate adjuvant (Fig. 12) and Al hydroxide adjuvant (Fig. 13) from the CDC vaccine schedule may cause toxicity from the solubilized Al per se.

Since 3.4mg/Kg/day is not a NOAEL (adverse effects were observed at this dosage) the true NOAEL is less than 3.4/mg/Kg/day. See Figs. 12-13.

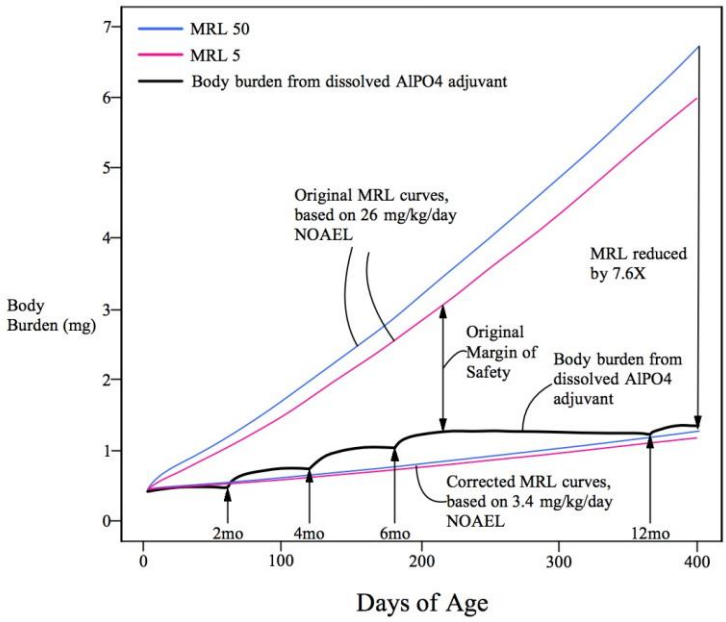

Fig. 12: Body burden vs. MRL comparison chart for Al <u>phosphate</u> adjuvant (AlPO4) corrected in accordance with the new discovery (Alawdi 2016) that ingestion of 3.4 mg/kg/day Al causes adverse effects. The body burden exceeds the corrected MRL curve for almost the entire first year of life, indicating toxicity. The toxicity of Al adjuvant <u>particles</u> is a separate, additional issue. MRL 50 and MRL 5 refer to two different infant growth rates. Adapted from Mitkus et al., 2011.

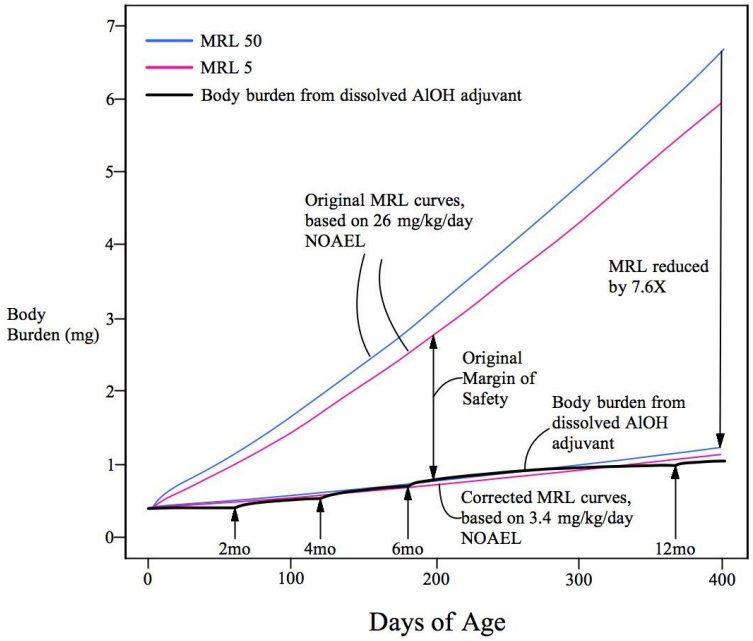

Fig. 13: Body burden vs. MRL comparison chart for Al hydroxide adjuvant (AlOH), corrected in accordance with the new discovery (Alawdi 2016) that ingestion of 3.4 mg/kg/day Al causes adverse effects. The body burden overlaps the new, corrected MRL, indicating borderline toxicity. The margin of safety is gone. MRL 50 and MRL 5 refer to two different infant growth rates. The toxicity of Al adjuvant particles is a separate, additional issue. Adapted from Mitkus et al., 2011.

3) NO AL ADJUVANT TOXICITY DATA CITED, DESPITE AVAILABILITY

Mitkus does not cite any toxicity data for injected Al adjuvants. Mitkus instead uses toxicity data for ingested, non-particulate, water-soluble Al (Golub 2001, which used Al lactate) to derive the MRL. This data comes from a single study (Golub 2001).

So, remarkably, Mitkus claims a safe level of injected Al adjuvant exposure, without citing any Al adjuvant toxicity data. The error is unnecessary and neglectful because at least two animal studies of injected Al adjuvant toxicity were available prior to the Mitkus publication in 2011 (Petrik 2007, Shaw 2009). These papers were not cited or mentioned by Mitkus 2011.

Each of these three flaws is fatal for the validity of the Mitkus study in establishing the safety of aluminum adjuvants. Hence, the CDC is completely lacking valid evidence for the safety of Al adjuvants. This is especially true for safety regarding neurological and long-term outcomes, because other available studies of Al adjuvant safety (e.g., Jefferson 2004) do not consider (or are incapable of detecting) these outcomes.

CDC Fails To Investigate Toxicity of Al Adjuvants

The CDC has conducted no epidemiological studies on long term safety (e.g. considering neurological outcomes) of Al adjuvants. There is one ecological study of country-level data, which reported an association between Al adjuvant exposure and autism (Tomljenovic 2011). However, being an ecological study, it is highly susceptible to confounding and biases.

Dr Frank DeStefano of the CDC's Immunization Safety Office is co-author of a

feasibility study (Glanz 2015) on using the Vaccine Safety Datalink (VSD) to investigate the safety of individual vaccine ingredients. The paper focuses on Al adjuvants. It acknowledges that thimerosal is the only vaccine ingredient studied for autism or neurological safety, and that a possible association between Al adjuvants and autism has not been explored in epidemiological studies. Glanz 2015 states:

> *"To date, there have been no population-based studies specifically designed to evaluate associations between clinically meaningful outcomes and non-antigen ingredients, other than thimerosal."*

The CDC has not investigated Al adjuvant safety concerns, despite the accumulating scientific evidence of harm and evidence linking Al adjuvants to immune activation mechanisms of brain injury.[1]

Conclusion

The science reviewed here tells a consistent and compelling story: that vaccines may cause autism by stimulating immune activation and elevated cytokines in the brain. Al adjuvants are implicated as a cause of autism because they can be transported into the brain, because they cause microglial activation at vaccine-relevant dosages, and because aluminum induces IL-6 in the brain.

In statements asserting no vaccine-autism link, the CDC cites scientific evidence that is not relevant to Al adjuvant safety or is incapable of disproving an Al adjuvant-autism link (Taylor 2014, DeStefano 2013, Mitkus 2011). In support of claims for Al adjuvant safety, the CDC relies on a profoundly flawed theoretical modelling study (Mitkus 2011). There is little scientific evidence supporting the safety of Al adjuvants, especially in relation to autism and other long term neurological outcomes.

[1] However, the Glanz paper notes that studies of aluminum adjuvants are problematic because of expected small differences in exposures in the low and high exposure groups. Glanz 2015 concludes: "*...children below the 10th percentile would be exposed to between 0 mg and 3.1mg, while children above the 90th percentile would be exposed to between 4.8 mg and 5.3 mg of aluminum from vaccines. It is unclear if such differences in aluminum exposure would be biologically meaningful.*" (Glanz 2015). So, epidemiological studies may not provide reliable evidence for safety or harm. Controlled, prospective human trials of aluminum adjuvant exposure from vaccines will likely be prohibited for ethical reasons. Also, Al adjuvants are essential ingredients for Al adjuvanted vaccines. Consequently, it will be challenging to design studies of long term adverse effects of Al adjuvants in humans. Experiments in animal models can provide valuable information. Al adjuvants should be tested for effects on: 1) excitatory/inhibitory imbalance; 2) core symptoms of autism (social, communicative and repetitive/stereotyped behaviors); 3) IL-6, IL-17, and other cytokine levels in the brain; 4) other physiological abnormalities associated with autism (e.g. mitochondrial dysfunction, microbiome dysbiosis, Purkinje cell loss, cerebellum abnormalities etc); and 5) microglial activation and immune activity in the brain. Investigating these outcomes can provide valuable information concerning the safety of Al adjuvants.

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