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Toxicology

Reconsideration of the immunotherapeutic pediatric safe dose levels of aluminum

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ABSTRACT

FDA regulations require safety testing of constituent ingredients in drugs (21 CFR 610.15). With the exception of extraneous proteins, no component safety testing is required for vaccines or vaccine schedules. The dosing of aluminum in vaccines is based on the production of antibody titers, not safety science. Here we estimate a Pediatric Dose Limit that considers body weight. We identify several serious historical missteps in past analyses of provisional safe levels of aluminum in vaccines, and provide updates relevant to infant aluminum exposure in the pediatric schedule considering pediatric body weight. When aluminum doses are estimated from Federal Regulatory Code given body weight, exposure from the current vaccine schedule are found to exceed our estimate of a weight-corrected Pediatric Dose Limit. Our calculations show that the levels of aluminum suggested by the currently used limits place infants at risk of acute, repeated, and possibly chronic exposures of toxic levels of aluminum in modern vaccine schedules. Individual adult exposures are on par with Provisional Tolerable Weekly Intake "limits", but some individuals may be aluminum intolerant due to genetics or previous exposures. Vaccination in neonates and low birth-weight infants must be re-assessed; other implications for the use of aluminum-containing vaccines, and additional limitations in our understanding of neurotoxicity and safety levels of aluminum in biologics are discussed.

1. Introduction

Aluminum is used as an adjuvant in vaccines licensed by the US Food and Drug Administration [1–7] to enhance the immunogenicity of the vaccine in various forms (e.g., aluminum oxyhydroxide and aluminum hydroxyphosphate) [9,10] (Fig. 1). The Center for Biologics Evaluation and Research (CBER) sets the amount of aluminum per dose in biological products, including vaccines, to 850 μg aluminum if measured by assay. Two additional levels are specified by the regulations (1140 and 1250 μg respectively), depending on how the level is measured [8].

The 850 μg of aluminum per vaccine FDA amount was derived from data that demonstrated that this amount of aluminum per dose enhanced the antigenicity and effectiveness of the vaccine [9,10], but does not include safety considerations. Current amounts of aluminum are not adjusted to body weight of an infant. To avoid toxicity associated with variation in body weight between adults and children related to aluminum in vaccines, standard of care dose levels convert mg to mg/kg for the weight range being considered [28,39]. At the current time, there are no known or published studies specifically defining levels of Al in any vaccine product based on safety studies of Al.

Safety for aluminum from all sources is based on the No Observed Adverse Effect Level (NOAEL), Minimal Risk Level (MRL), and the Lowest Observed Affect Level (LOAEL) [15–20]. The Joint Expert Committee on Food Additives (JECFA) established a Provisional Tolerable Weekly Intake (PTWI) for aluminum to be 7000 μg/kg body weight per week in 1989, which applies to all aluminum compounds in food, including additives. That level remained in effect until 2011 when the PTWI was revised to 2000 μg Al/kg per week [12,13]. The Agency for Toxic Substances and Disease Registry (ATSDR) had used an MRL of 1000 μg Al/kg per day (7000 μg/kg per week) [24–27].

We found two important errors in the provenance and derivation of provisional aluminum intake levels from World Health Organization (WHO; Supplementary Material) which, unfortunately, led to overestimation of safe exposure levels.

Here we consider adjusted child equivalent aluminum doses (CED) in vaccines by body weight, to determine putative pediatric dose limits

Abbreviations: NOAEL, no observed adverse effect level; LOAEL, lowest observed adverse effect level; MRL, minimal risk level; JECFA, joint expert committee on food additives; ATSDR, agency for toxic substances and disease registry; PTWI, provisional tolerable weekly intake; PDL, pediatric dose limit; CED, child equivalent dose; HED, Human Equivalent Dose

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Birth to 15 Months	(Adapted from "CDC Vaccine Schedules 2016")																
Vaccine	Aluminum Content (ug)* per dose	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos	18 mos	19-23 mos	2-3 yrs	4-6 yrs	7-10 yrs	11-12 yrs	13-15 yrs	16-18 yrs
Hepatitis B1 (HepB)	250	1st dose		2nd dose		3rd dose											
Rotavirus2 (RV) RV1 (2-dose series): RV5 (3-dose series)	0			1st dose	2nd dose												
Diphtheria, tetanus, & acellular pertussis3 (DTaP: <7 yrs)	625			1st dose	2nd dose	3rd dose				←4th dose→			5th dose				
Haemophilus influenzae type b4 (Hib)	225			1st dose	2nd dose			←3rd or 4th dose,									
Pneumococcal conjugate5 (PCV13)	125			1st dose	2nd dose	3rd dose		←4th dose→									
Inactivated poliovirus6 (IPV:<18 yrs)	0			1st dose	2nd dose	←3rd dose→							←4th dose→				
Influenza7 (IIV: LAIV)	0					Annual vaccination (IIV only) 1 or 2 doses				Annual vaccination (IIV only) 1 or 2 doses		Annual vaccination (IIV only) 1 or 2 doses			Annual vaccination (IIV only) 1 or 2 doses		
Measles, mumps, rubella8 (MMR)	0							1st dose					2nd dose				
Varicella9 (VAR)	0							1st dose					2nd dose				
Hepatitis A10 (HepA)	250							1st dose		2nd dose							
Meningococcal11 (Hib-MenCY ≥ 6 weeks; MenACWY-D ≥9 mos; MenACWY-CRM ≥ 2 mos)	0														1st dose		
Tetanus, diphtheria, & acellular pertussis12 (Tdap: ≥7 yrs)	330														(Tdap)		
Human papillomavirus13 (2vHPV:females only; 4vHPV, 9vHPV:males and females)	0														(3 dose series)		
Meningococcal B11	0																
Pneumococcal polysaccharide5 (PPSV23)	Unknown																
	* Total ug not adjusted to ug/kg	250		1225	975	1000		600		875							

Fig. 1. Pediatric Vaccine Schedule 2016–2017.
The CDC schedule reflects the expected timing of administration of vaccines containing aluminum (shaded light yellow) as adjuvant at birth, 2, 4, 6, 12, and 18 months. The total amount of aluminum per vaccine visit (green shaded box below each scheduled interval) is reported from birth through 24 months.

(PDLs) of aluminum estimated by Clark's Rule for the pediatric population, to investigate further the effect those discrepancies that exist between the JECFA and ATSDR may have regarding the MRL of aluminum in biologics, and to compare relative dosing from dietary and injected sources in the pediatric population.

2. Materials and methods

2.1. FDA dose amounts of aluminum adjusted by body weight in infants and adults

FDA regulations require that proteins in vaccines be tested for safety. Aluminum is a known neurotoxin and it is unfortunate that additives in vaccines are not required to be subjected to animal safety studies prior to use on human subjects. Several known methods exist for pediatric dosing by weight. In Clark's Rule [28–39] of pediatric dose calculations, for example, the adult body weight reference is usually (as published) considered to be 150 bs. (68 kg) with the calculated dose being converted to mg/kg.

Aluminum toxicity studies use 60 kg as the reference adult body weight to calculate the MRL and LOAEL [16–18]. For that reason, we used 60 kg as the adult body weight reference rather than the more commonly used 68 kg adult body weight reference in Clark's Rule of pediatric calculations. Our calculations are thus consistent with past aluminum toxicity studies [16–18], and more comparable to the toxicities at the No Observed Adverse Effect Level (NOAEL) and Lowest Observed Adverse Effects Level (LOAEL).

Each of the established FDA-approved doses of 850 μg, 1140 μg, and 1250 μg were converted to the equivalent dose expressed in mg/kg using Clark's Rule [28,39]:

$$Child's\ Dose\ (\text{mg}) = Adult\ Dose\ (\text{mg}) \times \frac{BW\,(Child)lbs}{BW\,(Adult)lbs}$$

The body weights for infants from birth through 24 months used in the Clark's Rule calculation were obtained using calculated monthly growth velocities obtained from Weight for Age standards in males and females from the 5th to the 95th percentile [40,41]. The resulting pediatric doses were compared to the same doses in an adult also adjusted by the body weight of 60 kg.

2.2. Minimal risk level of aluminum in children

Minimal Risk Levels (MRLs) are usually derived for hazardous substances using the NOAEL/uncertainty factor approach [16,17] to avoid toxicities [21]. The resulting exposures using the adjusted body weight calculations are presented by plotting the calculated MRL in children against the FDA doses of 850 μg adjusted by body weight at the 50th percentile in children birth through 24 months.

We estimated the human equivalent dose (HED) [11,20,21] in a child first obtaining the adult HED using the equation

HED = Animal dose NOAEL (mg/kg) × [Animal weight (kg)/Human weight (kg)]$^{(1 - \text{BSA exponent } 0.67)}$

The HED of the NOAEL/MRL may be calculated using a K_m ratio or Rule of Exponents equation [21] with a provisional additional safety factor of 10 applied. The results of these two calculations differ significantly. The anatomic compartment from which exogenous aluminum is absorbed also needs to be taken into consideration (intestinal vs. intramuscular).

The animal dose reference used by the ATSDR is 260 μg/kg and the reference animal weight of the mouse is 0.02 kg [15]. The adult human body weight reference used was 60 kg to be consistent with the previous ATSDR calculations of MRL [16,17]. A safety factor of 10 is applied to the final calculation of the adult HED to obtain the Minimal Risk Level (MRL) for an adult human [21].

To obtain the Child Equivalent Dose (CED) of the adult MRL, we multiplied the $MRL_{(adult)}$ by the body weight ratio between child and adult:

$$\text{CED (mg/kg)} = \text{HED}_{(adult)} \text{ mg/kg} \times \text{BW}_{(child)} \text{ (kg)}/\text{BW}_{(adult)} \text{ (kg)}$$

Additionally, we calculated the pediatric equivalent of the daily provisional tolerable intake using the JECFA adult reference of 286 μg (2 μg/kg per week JECFA provisional tolerable weekly intake divided by 7 days converted to micrograms) to establish a revised and corrected provisional tolerable daily intake from the weekly intake adjusted by the BW of the child at the 5th through the 95th percentile from birth to 24 months. It should be recalled that animal levels (ATSDR and JECFA MRL) contributing to these revised estimated levels were based on enteral (dietary) exposures, and in adult animals.

The only available safety dosing reference point for for large—and small—volume parenteral exposures of aluminum is from CFR/FDA 21CFR201.323 from intravenous exposure. That safety limit is placed at 4–5 μg/kg/day, without reference to duration of treatment and applies to individuals with renal dysfunction, a condition that is very common among premature infants.

3. Results

3.1. FDA doses adjusted by body weight in infants and adults

Each of the FDA doses for aluminum (850 μg, 1100 μg, and 1250 μg) were divided by the daily body weights per percentile weight class by age from birth to 2 years and expressed as μg/kg. Similarly, these same dose limits were divided by the adult body weights of 60 kg for comparison (μg/kg).

3.2. FDA 850 μg dose adjusted by body weight in infants and adults

If infants were given 850 μg of aluminum (injected), the exposure would vastly exceed the only available CFR/FDA 4–5 μg/kg/day safety limit (Fig. 2). Compared to an adult whose body weight is 60 kg, a male child at birth receives 254 μg/kg, 152.7 μg/kg at 2 months, 121.4 μg/kg at 4 months, 107.1 μg/kg at 6 months, 92.8 μg/kg at 1 year, and 69.9 μg/kg at 2 years as compared to 12.5-14.2 μg/kg in an adult. A female child whose body weight is generally less than the male receives a slightly higher burden of aluminum comparatively. At the 50th percentile body weight, a male child at birth receives 1800% more aluminum per body weight as compared to a 60-kg adult male, 1074.6% at 2 months, 954.9% at 4 months, 754.2% at 6 months, 876% at 1 year, and 493% at 2 years of age more aluminum per body weight as compared to a 60-kg adult (Table 1, Fig. 2).

3.3. FDA 1140 μg dose adjusted by body weight in infants and adults

Compared to an adult whose body weight is 60 kg, a male child at birth receives 340.7 μg/kg, 204.8 μg/kg at 2 months, 162.8 μg/kg at 4 months, 143.7 μg/kg at 6 months, 124.4 μg/kg at 1 year, and 93.8 μg/kg at 2 years as compared to 16.8-19.0 μg/kg in an adult. Similarly, a female child whose body weight is generally less than the male receives a slightly higher burden of aluminum comparatively.

3.4. FDA 1250 μg dose adjusted by body weight in infants and adults

Compared to an adult whose body weight is 60 kg, a male child at birth receives 373.5 μg/kg, 224.5 μg/kg at 2 months, 178.5 μg/kg at 4 months, 157.5 μg/kg at 6 months, 136.4 μg/kg at 1 year, and 102.9 μg/kg at 2 years as compared to 18.4-20.8 μg/kg in an adult. Similarly, a female child whose body weight is generally less than the male receives a slightly higher burden of aluminum comparatively.

3.5. Comparison of FDA dose adjusted by body weight between infants and adults

To define an appropriate modification in the amount of aluminum per dose in a pediatric vaccine, and separate from the previous HED based upon the MRL, we applied Clark's Rule at both 68 kg and 60 kg to the 850 μg FDA dose by assay (0.85 mg per dose by assay). The calculated 850 μg per dose at the 50th percentile is lower when converting the adult body weight reference to 60 kg, the adult body weight typically used in toxicity studies (Fig. 3).

At birth, and in consideration of Clark's Rule in pediatric dosing (Adult BW = 68 kg), these calculations, based on assumptions, suggest that a child at the 50th percentile BW should receive no more than 44 μg/kg. That modification in the actual amount of aluminum per dose of a pediatric vaccine (or vaccines per day) should be at or below the current adult-based, diet-based MRL. Unfortunately, that would exceed the calculated MRL of 10.31 μg/kg at birth, and 37.48 μg/kg at 2 years of age.

3.6. Aluminum daily minimal risk level (MRL) in children, all sources with applied safety factor

In an adult weighing 60 kg whereby the human K_m is 37 and mouse K_m is 3 (K_m ratio = 0.081), the Minimal Risk Level (MRL) of 26 mg Al/kg mouse dose (26) would be 26 × 0.081 = 2.11 mg/kg/day. Applying the safety factor of 10 would correct the MRL to 0.21 mg/kg/day, not 1 mg/kg/day. The application of an additional safety factor of 10 is the accepted final step prior to establishing first dose during trial dosing 12,13,15-20].

The K_m in an 8-year-old child weighing 20 kg is 25 [15]. The calculated pediatric HED of the Minimal Risk Level (MRL)/NOAEL using the K_m ratio formula would be 26 mg/kg times 0.12 (K_m ratio = 3/25) divided by the safety factor of 10 would result in an HED of 3.12 mg Al/kg before a safety factor of 10 is applied using the K_m ratio. With the safety factor of 10, the estimated MRL would be 312 μg Al/kg/day in an 8-year-old child weighing 20 kg. That would effectively lower the ATSDR MRL estimate from 1000 μg Al/kg day to 312 μg Al/kg/day by a factor of 3.2 with the safety factor applied.

Without a provisional safety factor, the MRL would be greater than the ATSDR provisional tolerable daily intake of 1 mg Al/kg per day, but less than the JECFA provisional tolerable daily intake of 290 μg Al/kg which is a concern. With the safety factor of 10, the estimated MRL in the pediatric population (< 8 years of age) is less than the 500 μg/kg body weight from all sources including additives range 100–350 μg/day identified in the JECFA report regarding children 2 years of age.

3.7. MRL based upon rule of Exponents/Safety factor of 10

In consideration that the HED calculated by the K_m ratio may not be appropriate for use in intramuscular exposures [22,23], we used the Rule of Exponents equation [21]

HED = Animal dose NOAEL (mg/kg) × [Animal weight (kg)/Human

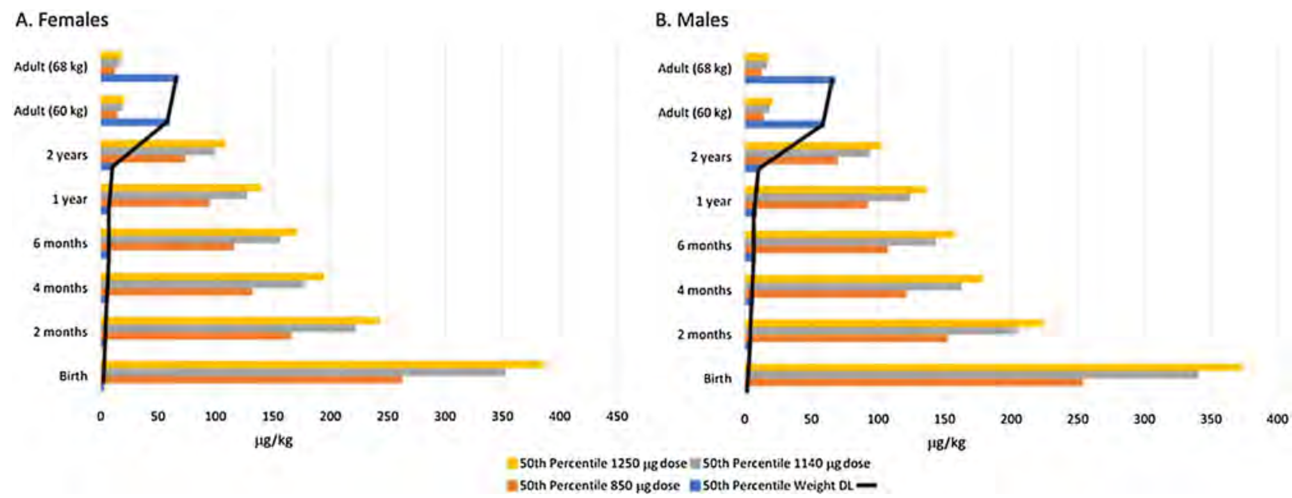

Fig. 2. FDA Doses and exposures adjusted by body weight: Comparison between Infants and an Adult.
In a male child from birth through 36 months at the 50th percentile body weight, the FDA dose of 850 µg adjusted by body weight demonstrates that an adult weighing 60 kg receives significantly less aluminum per injection per kg compared to a child, particularly those children with lower body weights.

Table 1
FDA Dose Adjusted by Body Weight (µg/kg), Birth through Adulthood, US Population.

MALES (50th Percentile Body Weight)				
Age	Body Weight (kg)	850 µg dose (µg/kg)	1140 µg dose (µg/kg)	1250 µg dose (µg/kg)
Birth	3.35	254.00	340.66	373.54
2 months	5.57	152.67	204.76	224.52
4 months	7.00	121.39	162.80	178.51
6 months	7.93	107.13	143.67	157.55
1 year	9.17	88.10	118.16	129.56
2 years	12.15	69.95	93.82	102.87
Adult Reference (60 kg)	60	14.17	19.00	20.83
Adult Reference (68 kg)	68	12.5	16.76	18.38
FEMALES (50th Percentile Body Weight)				
Age	Body Weight (kg)	850 µg dose (µg/kg)	1140 µg dose (µg/kg)	1250 µg dose (µg/kg)
Birth	3.23	262.98	352.70	386.73
2 months	5.13	165.75	222.30	243.75
4 months	6.42	132.32	177.47	194.59
6 months	7.29	116.49	156.23	171.30
1 year	8.95	94.99	127.40	139.69
2 years	11.48	74.06	99.92	108.91
Adult Reference (60 kg)	60	14.17	19.00	20.83
Adult Reference (68 kg)	68	12.5	16.76	18.38

weight (kg)]$^{(1 - \text{BSA exponent } 0.67)}$

In an adult weighing 60 kg, the calculated HED using the above equation would be 1850 µg/kg without a safety factor of 10. Applying the safety factor of 10 would result in the HED (MRL) of 185 µg/kg, significantly lower than the current ATSDR MRL/NOAEL of 1000 µg Al/kg/day. This approximates the corrected 2007 JECFA calculation of 140 µg/kg/day (PTWI of 1000 µg Al/kg per week).

We do not mean to imply this level exposure is safe for pediatric injection. The corresponding HED in a child should take into consideration the ratio of the $BW_{(child)}/BW_{(adult)}$, such that $MRL_{(child)}$ = Adult MRL(mg/kg) X $BW_{(child)}/BW_{(adult)}$.

At birth, for 50th percentile body weight males the daily MRL would be 16.01 µg/kg/day (0.01601 mg/kg/day) and 58.12 µg/kg/day at 2 years (See Supplemental Files). As expected, a female child would have a corrected value of 15.46 µg/kg/day at birth and 54.9 µg/kg/day at 24 months. In a child, that recalculated MRL would be less than the 1989 JECFA provisional tolerable daily intake from dietary and additive exposures of 140 µg/kg/day and current provisional tolerable daily intake of 290 µg/kg/day per day both before and after the safety factor of 10 is applied (Fig. 3).

As an example, using a specific vaccine, the weight-adjusted MRLs and aluminum exposures from DTaP vaccine (with 625 µg aluminum per dose) show exposures in children at 2 months that vastly exceed the dietary adult mouse-derived MRL considering body weight (Fig. 4).

4. Discussion

Aluminum in various forms is commonly used as an adjuvant in many vaccines licensed by the US Food and Drug Administration [1–7]. In 2002, the scheduled childhood vaccines that included aluminum as an adjuvant were limited to Diphtheria-Pertussis-Tetanus (DPT) and Hepatitis B (HepB). The amount of aluminum per vaccine dose ranged from 250 µg/dose (HepB) to 625 µg/dose (DPT). In 2016, however, the number of individual pediatric vaccines containing aluminum as adjuvant from birth to 36 months has increased significantly and ranges from 250 to 625 µg/dose [3–6] (Table 1; Fig. 1). Those vaccines, which contain aluminum as an adjuvant to increase antigenicity [33,34] include Hepatitis B (HepB)[2], Diphtheria, Tetanus, acellular Pertussis (DTaP) [3], Haemophilus influenza B (HiB) [4], Hepatitis A (HepA) [5], and pneumococcal conjugate (PCV13) [6]. Here, we further discuss the background and provenance of the derivation of aluminum doses, issues that may be currently causing unanticipated dose-related toxicity.

The FDA referenced doses of 850 µg, 1140 µg, and 1250 µg have not been estimated considering body weight of the pediatric population, nor do they necessarily directly reflect established non-toxic doses in that population prior to this report. The current aluminum amounts in vaccines are not sufficiently characterized: the doses of aluminum used in vaccines, and the per day exposure that results from the CDC vaccine schedule, are not determined based on animal dose escalation safety (NOAEL) studies. They are also determined considering neither injected dose-related toxicity, nor mass differences between adults and infants. This issue must be addressed.

Our results demonstrate that the aluminum exposure from vaccines would exceed the calculated Pediatric Dose Limit, or PDL 850 µg aluminum/dose by assay, when corrected to 44 µg by Clark's Rule estimated from the FDA adult dose of 850 µg/dose (850 µg x $BW_{(child)}$ 3.35/$BW_{(Adult)}$ 68 kg) at birth, 2.5, 4.5, and 6.5 months. It must be emphasized that at birth, only the aluminum content in the HepB vaccine is under consideration. Only at 6.5 months does the combined aluminum

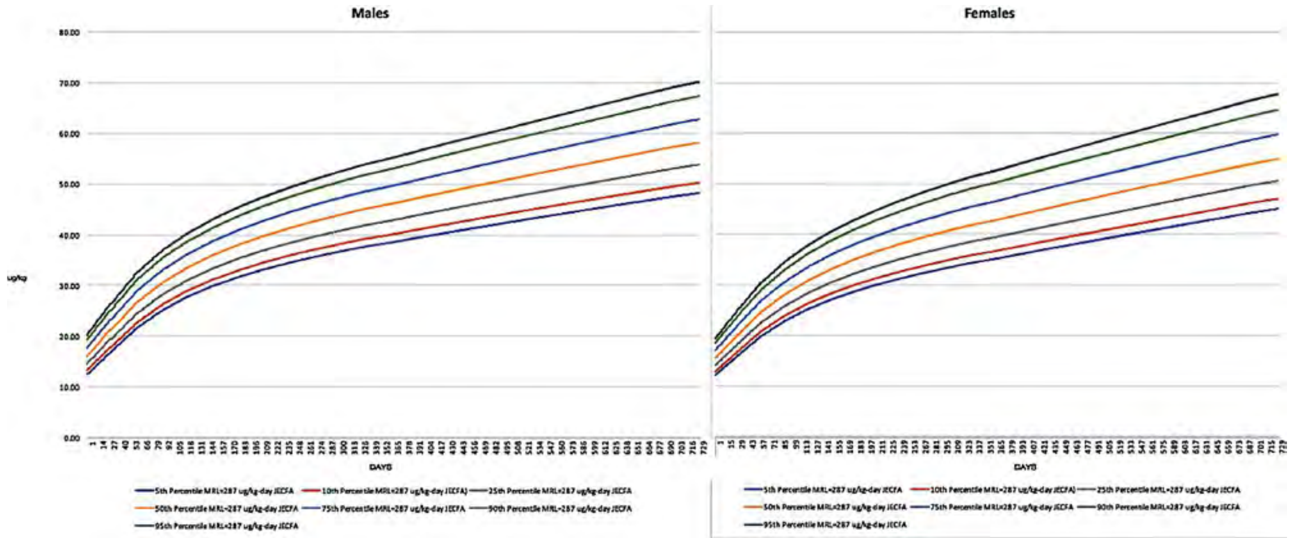

Fig. 3. MRL Males and Females, Birth-24 years (5th-95th Percentile Body Weight).
The most recent daily JECFA MRL of 287 µg/kg/day in a child from birth through 24 months (729 days) was calculated by multiplying the daily Child BW/Adult BW ratio using a referenced adult body weight of 60 kg and the daily child body weight at the 5th-95th percentile. The final calculation is expressed in µg/kg/day (Y-axis). The 50th percentile body weight daily calculation is demonstrated with the orange line (see Legend at bottom of graph).

level fall below the 1140 and 1250 µg/kg calculated dose level at the 50th percentile body weight. This is a clearly significant concern for the current vaccine schedule, especially in the context of the recommended (and increasingly strongly enforced) time intervals at birth, 2, 4, and 6 months.

All individual doses are at or below the FDA dose of 850 µg/dose by assay. However, when administered simultaneously at the recommended CDC schedule, the "limit" is significantly exceeded if not modified in accordance with standard pediatric dose calculations. These doses are given regardless of body weight. The product data sheet for DTaP states, for example:

> "Each 0.5-mL dose contains aluminum salts as adjuvant not more than 0.85 mg (850 µg) aluminum by assay"

When adjusted to body weight (µg/kg) and compared to a 60–68 kg adult, the aluminum load is significantly higher in the birth through 24-month age cohort.

The scheduled pediatric vaccinations in 2016 have significantly expanded since 2002, and the amount of aluminum per vaccine dose, particularly the use of TDaP, has changed. The combined doses of aluminum at 2, 4, and 6 months are 1225 µg, 975 µg, and 1225 µg respectively (Table 2), and are not determined considering infant and

Table 2
ATSDR References for NOAEL and LOAEL.

Population	Year Published	Route of Exposure	NOAEL	LOAEL	Reference
Mice	1989	Dietary	62 mg Al/kg	130 mg Al/kg	Golub et al. [24]
Mice	2001	Dietary	26 mg Al/kg	130 mg Al/kg	Golub et al. [25]
Mice	2005	Dietary	53 mg Al/kg	103 mg Al/kg	Colomina et al. [26]
Mice	2000	Dietary	–	100 mg Al/kg	Golub et al. [27]

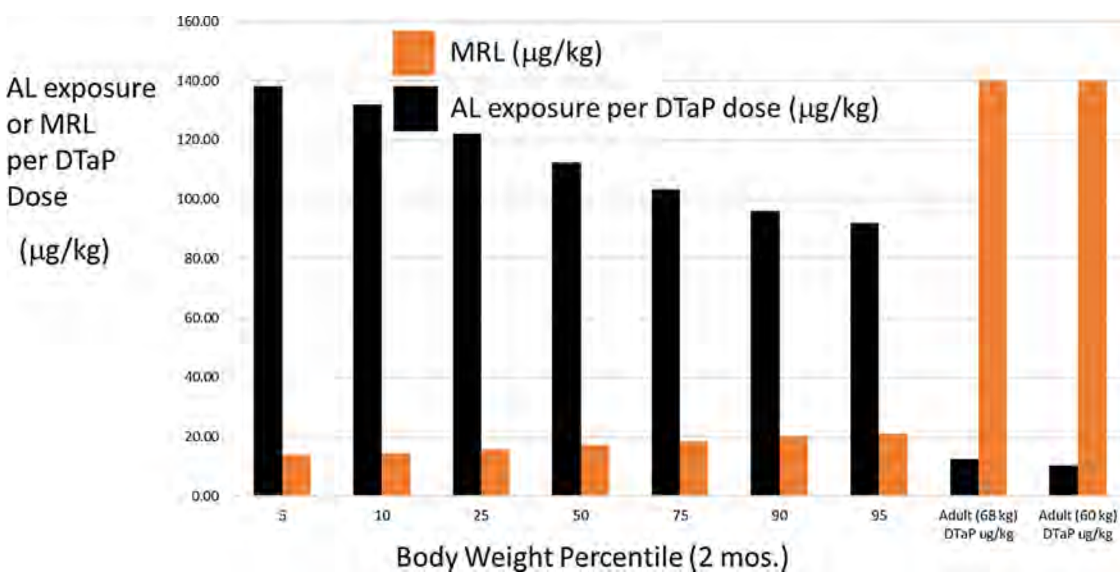

Fig. 4. Comparison of the Calculated Pediatric MRL and the AL Exposures from DTaP Vaccine for Children (and Adults) using Clark's Rule to Accommodate Pediatric Body Weights (µg/kg, per day, at 2 months and for Adult).

child body weight.

When expressed considering infant and child body weight ($BW_{(child)}$) obtained from the CDC growth data sheets, the individual aluminum levels (μg/kg) in the HepB, DTaP, Hib, and PCV vaccines remain below the limits of 850 μg/kg, 1440 μg/kg, and 1225 μg/kg at birth. However, at 2.5 months, 4.5 months, and 6.5 months, the combined aluminum levels (μg/kg) in the scheduled DTaP, HiB, and PCV vaccines exceed the FDA 850 μg limit by a factor of 1.15.

4.1. The PTWI propagated error

In our review of the provenance of information on Al limits, we discovered an unfortunate but serious error in the calculation in the MRL. The JECFA established a PTWI for aluminum to be 7000 μg/kg body weight per week in 1989. The PTWI applied to all aluminum compounds in food, including additives which remained in effect until 2011. The provisional tolerable daily intake (all sources) would therefore have been around 1000 μg/kg/day.

From 1989 to 2011, the MRL was reported to be 1000 μg/kg/day from all sources. That number was withdrawn in 2011, therefore the total provisional tolerable daily intake should be currently 0.29 mg Al/kg per day, based upon the provisional tolerable weekly intake (PTWI) of 2 mg Al/kg week as expressed by the Joint Food and Agriculture Organization of the United Nations and World Health Organization (FAO/WHO) Expert Committee on Food Additives (JECFA) in 2011.

In 1996, the Committee on Nutrition in their article on aluminum neurotoxicity in children reported the 1989 JECFA provisional tolerable weekly intake of 1000 μg/kg [12] as a provisional daily intake [14]. Unfortunately, that error overestimates the provisional tolerable daily intake of aluminum from all sources in adults by a factor of at least 2. As the 1000 μg/kg/week PTWI was in fact replaced with a PTWI of 2000 μg/kg/week in 2011, the daily provisional tolerable intake should be around 286 μg/kg per day, and in consideration that the highest mean intake of a child at 2 years is 500 μg/kg per day [15]. The value 1000 μ/kg/day would seem to bring the 850 μg per dose into range, but it is off by a factor of at least 2 and perhaps seven. The role of the reliance on the incorrect PTWI on public health may be significant, especially for infants, especially for low-birthweight infants and those born prematurely.

By our calculations, and in consideration of the route of exposure using the Rule of Exponents to calculate the HED, the correct daily (all sources, all doses) MRL in the pediatric population should have been determined to be no more than 10.31-16.01 μg/kg per day at birth to 58.12 μg/kg per day at 2 years of age. Current exposures from pediatric vaccines exceed these levels; for a median weight (US) 3.3 kg male, HepB vaccine with 250 μg leads to 75.75 μg/kg/day. The two-month vaccination visit repeats the excess. Excess exposures in low birthweight and neonatal infants is obviously even more problematic. The use of HepB vaccine in a 2-kg infant (FDA's unofficial cut-off for vaccination in the Neonatal Intensive Care Unit, NICU) leads to 150 μg/kg/day. Vaccination practices in the NICU must be revisited.

Our results demonstrate that the aluminum load from vaccines would exceed the estimated PDL 850 μg aluminum/dose by assay, when corrected to 47.4 μg by Clark's Rule estimated from the Federal adult dose limit of 850 μg/dose (850 μg x $BW_{(child)}$3.35 kg/$BW_{(Adult)}$ 68 kg) at birth to 24 months. The adjusted dose limits would still be higher than the calculated MRL per day.

The NOAEL and LOAEL have been established to reduce the incidence of known harmful neurotoxic effects and are based on studies of adult mice using poorly-absorbed, ingested aluminum not highly-absorbed injected aluminum. The entire paradigm to aluminum dosing in vaccines has not been determined considering body weight, based on NOAEL (not the LOAEL), which is more in line with the universal standard medical practices during pediatric dosing [28,39]. These should be calculated per child given their body weight prior to vaccination, and daily limits placed on total aluminum injected considering all doses and all sources. However, even when the appropriate and necessary adjustments are made, our results predict an increased risk of neurotoxicity from birth through 36 months particularly when the accumulating body burden is taken into consideration at every scheduled vaccine interval. Although not considered in this current analysis, we are aware that the accumulated aluminum body burden at each vaccination interval will be higher than an individual aluminum level in a single vaccine. This is because there will be a retained body burden fraction of aluminum resulting from the previous dosing intervals considering body weight (in progress) that needs to be considered, particularly in consideration of potential toxicities.

Mitkus et al. [32]'s calculations were based on the day/week propagated error. Mitkus et al. [32] published their study in 2011 when the PTWI was still at 1 mg/kg, further propagating the day/week error. Thus, current assessments of aluminum accumulation from vaccination and dietary exposures are not correct. Some dietary sources contain unacceptably high levels of aluminum, such as certain brands of antacids. Concerned individuals can exercise consumer choice and avoid food products that include aluminum.

While the effect of our proposed reduction on the final antigenicity of the vaccine is unknown, the full effects of the high injected doses of aluminum on the developing brain are also unknown. Indications of accumulation of aluminum associated with autism were recently published [42] in which the majority of tissue samples from post-mortem brains of patients diagnosed with autism spectrum disorder (ASD) were found to contain high concentrations of aluminum. Many samples contained extremely high concentrations, and the study also localized aluminum in glial cells in the brain, consistent with aluminum-induced gliosis models of neurodevelopmental disorders.

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Conflict of interest

RR has no real or potential conflict of interest. JLW has a potential conflict of interest as he has consulted on two vaccine injury cases on behalf of complainants.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jtemb.2018.02.025.

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