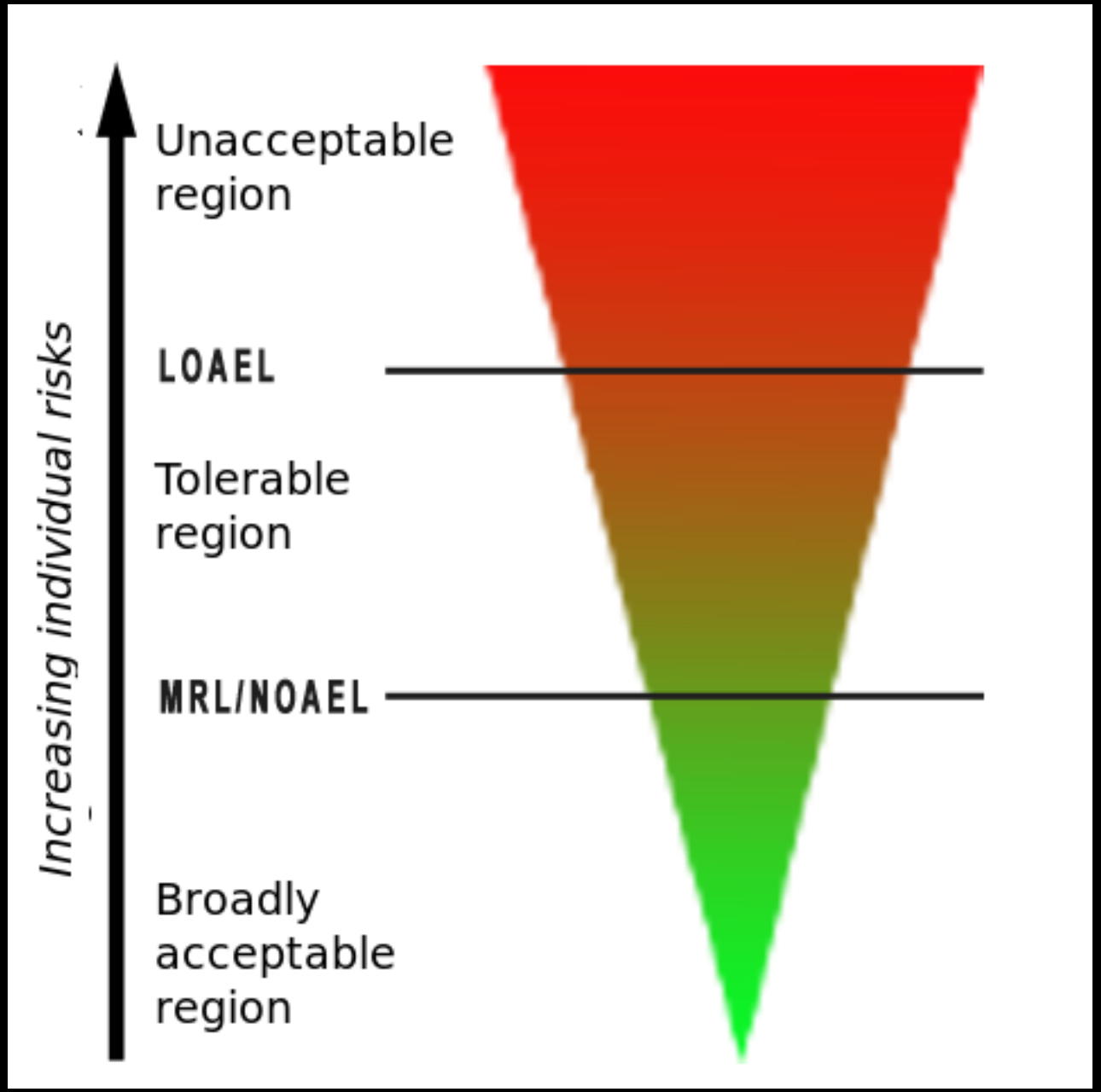
Comparison of Aluminum Dosing Human Vaccines and Animal Autoimmune Studies

James Lyons-Weiler, PhD

INSTITUTE FOR PURE AND APPLIED KNOWLEDGE

Wednesday, May 16, 2018


FDA


Unacceptable region
LOAEL
Tolerable region
MRL/NOAEL
Broadly acceptable region
Increasing individual risks

Policy Analysis: What the FDA Has Said About Aluminum in Vaccines

- *"we have demonstrated that aluminum levels in infants are well below the minimal risk level curves for either median or low-birth weight babies"* – Mitkus et al, 2011 (Vaccine)

- *"When evaluating a vaccine for safety and efficacy, FDA considers adjuvants as a component of the vaccine; they are not licensed separately"* – US FDA Website https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm175909.pdf

- *"An adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety or potency of the product. 21CFR610.15"*

FDA Web page reviewing Mitkus et al (2011)

- *The risk to infants posed by the total aluminum exposure received from the entire recommended series of childhood vaccines over the first year of life is extremely low;*
- *Using the updated parameters, the authors found that the body burden of aluminum from vaccines and diet throughout an infant's first year of life is significantly less than the corresponding safe body burden of aluminum, based on the minimal risk levels established by the* ***Agency for Toxic Substances and Disease Registry***

- https://www.fda.gov/BiologicsBloodVaccines/ScienceResearch/ucm284520.htm

Journal of Trace Elements in Medicine and Biology 48 (2018) 67–73

Contents lists available at ScienceDirect

Journal of Trace Elements in Medicine and Biology

journal homepage: www.elsevier.com/locate/jtemb

Toxicology

Reconsideration of the immunotherapeutic pediatric safe dose levels of aluminum

James Lyons-Weiler[a,*], Robert Ricketson[b]

[a] Institute for Pure and Applied Knowledge, 2912 Kilcairn Lane, Allison, PA 15101, United States
[b] Hale O'mana'o Research, 19 West Edwards Street, Edmond, OK 73003, United States

ARTICLE INFO

Keywords:
Aluminum
Minimum risk level

ABSTRACT

FDA regulations require safety testing of constituent ingredients in drugs (21 CFR 610.15). With the exc
extraneous proteins, no component safety testing is required for vaccines or vaccine schedules. The c
aluminum in vaccines is based on the production of antibody titers, not safety science. Here we es

Problems with Mitkus et al. (2011)

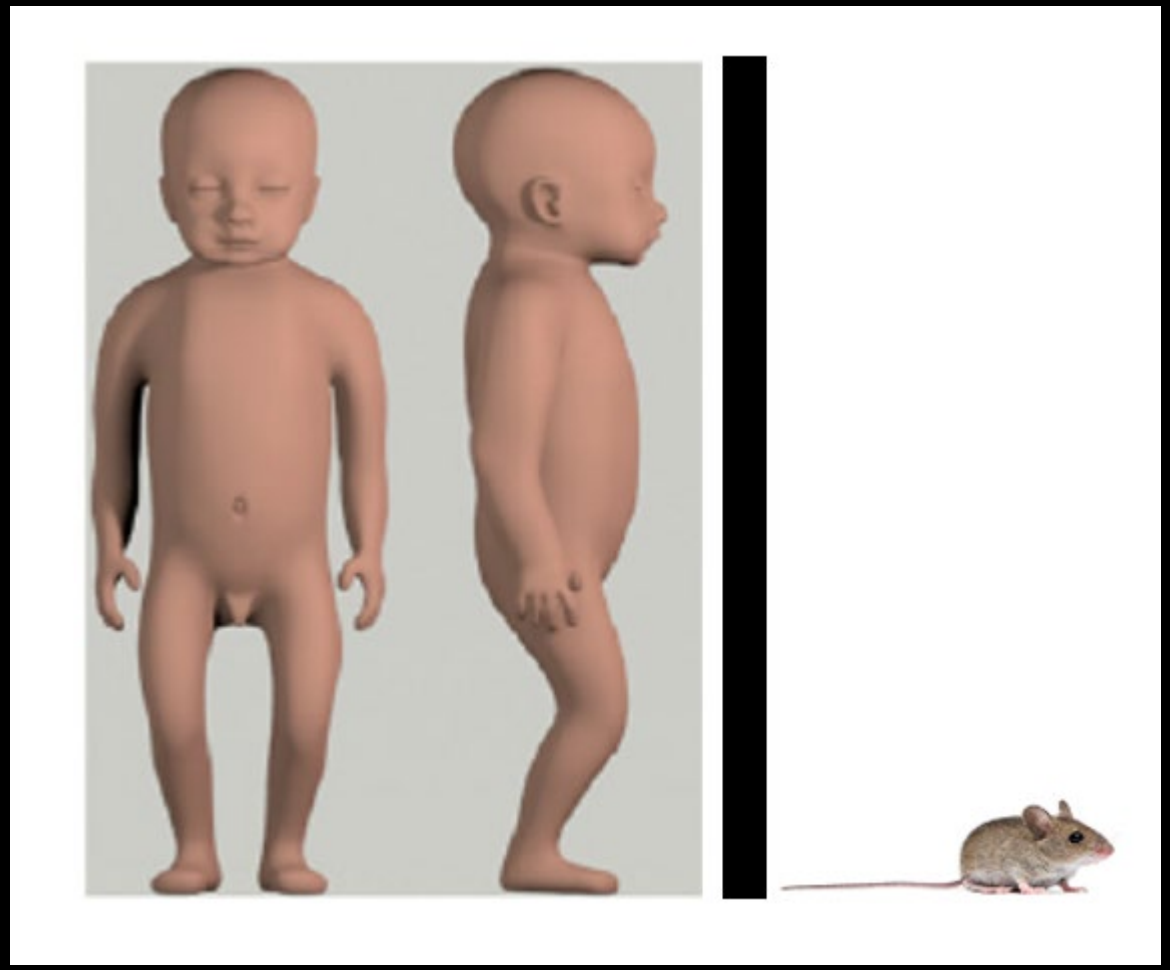
- Based toxicity assessment of injected forms of aluminum on MRLs from DIETARY EXPOSURES in ADULT ANIMALS
- Estimated compartmental toxicity as if whole-body toxicity
- Used MRLs arbitrarily selected by HHS (ATSDR) of 1 mg/kg/day

based on 1 study (Golub et al), ignoring other studies

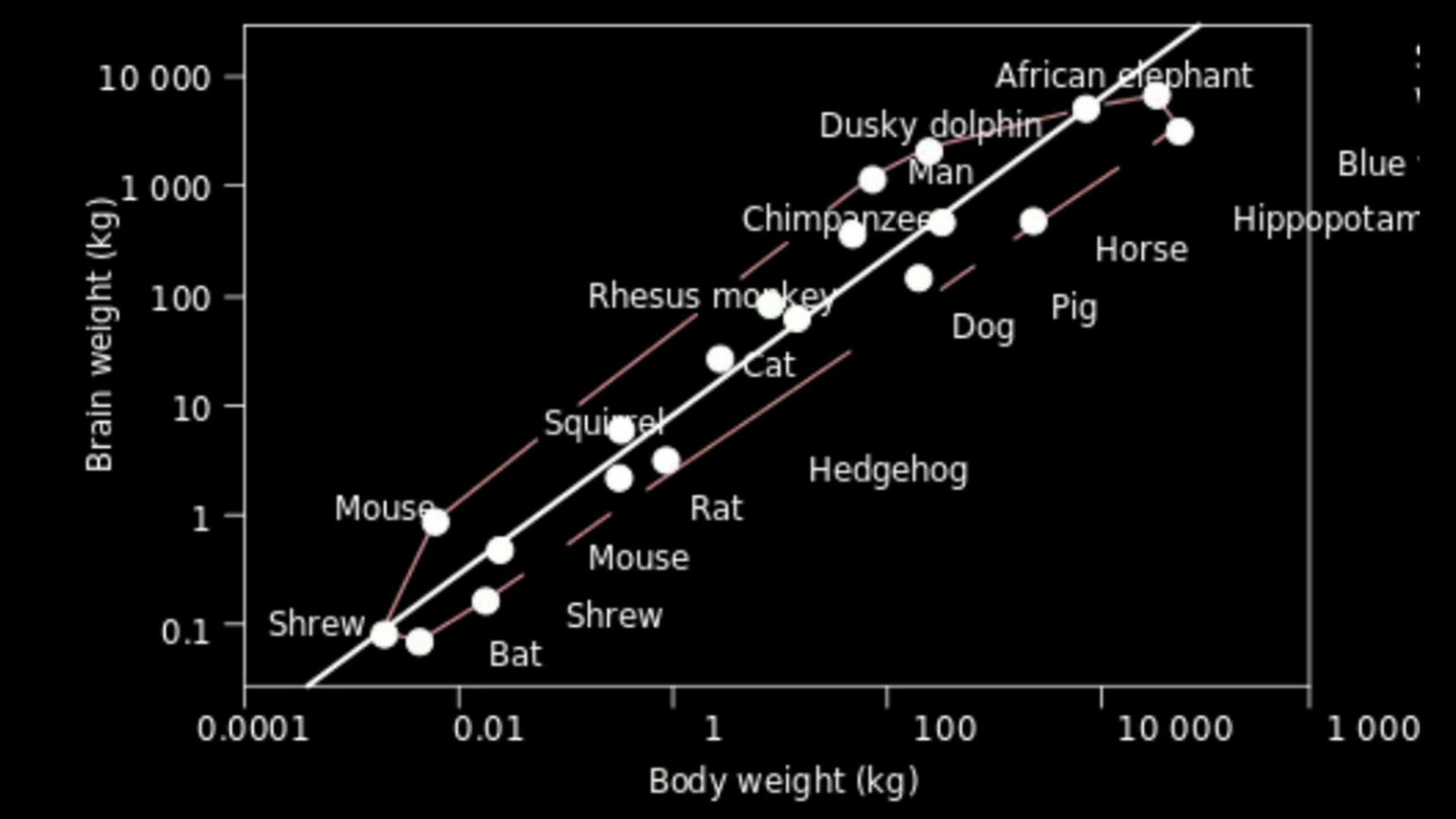
- JEFCA (WHO) had an MRL of 2 mg/kg/day, previously published MRL of 1 mg/kg/day (all sources)

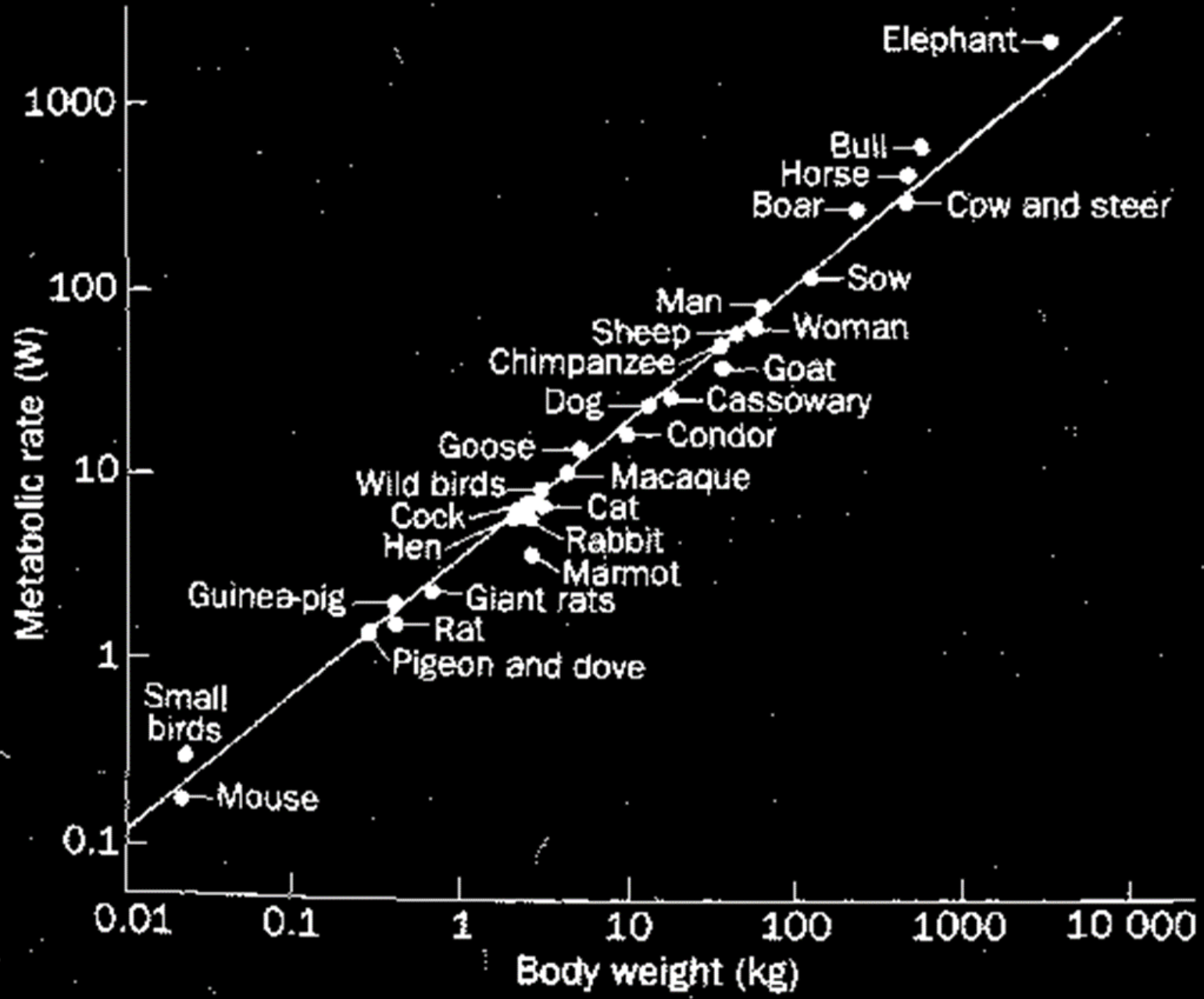
Diet vs. Injection

Adult Mouse vs. Adult Human
20 vs. 4 inches



Newborn brain 375 g
Adult mouse brain 0.4 g
1000-fold smaller


10 000
1 000
100
10
1
0.1
Brain weight (kg)
African elephant
Dusky dolphin
Man
Blue
Chimpanzee
Hippopotam
Horse
Rhesus monkey
Pig
Dog
Cat
Squirrel
Hedgehog
Mouse
Rat
Mouse
Shrew
Shrew
Bat
0.0001
0.01
1
100
10 000
1 000
Body weight (kg)


Elephant
Bull
Horse
Boar
Cow and steer
Sow
Man
Woman
Sheep
Chimpanzee
Goat
Dog
Cassowary
Condor
Goose
Macaque
Wild birds
Cat
Cock
Rabbit
Hen
Marmot
Guinea-pig
Giant rats
Rat
Pigeon and dove
Small birds
Mouse
1000
100
10
1
0.1
Metabolic rate (W)
0.01
0.1
1
10
100
1000
10 000
Body weight (kg)

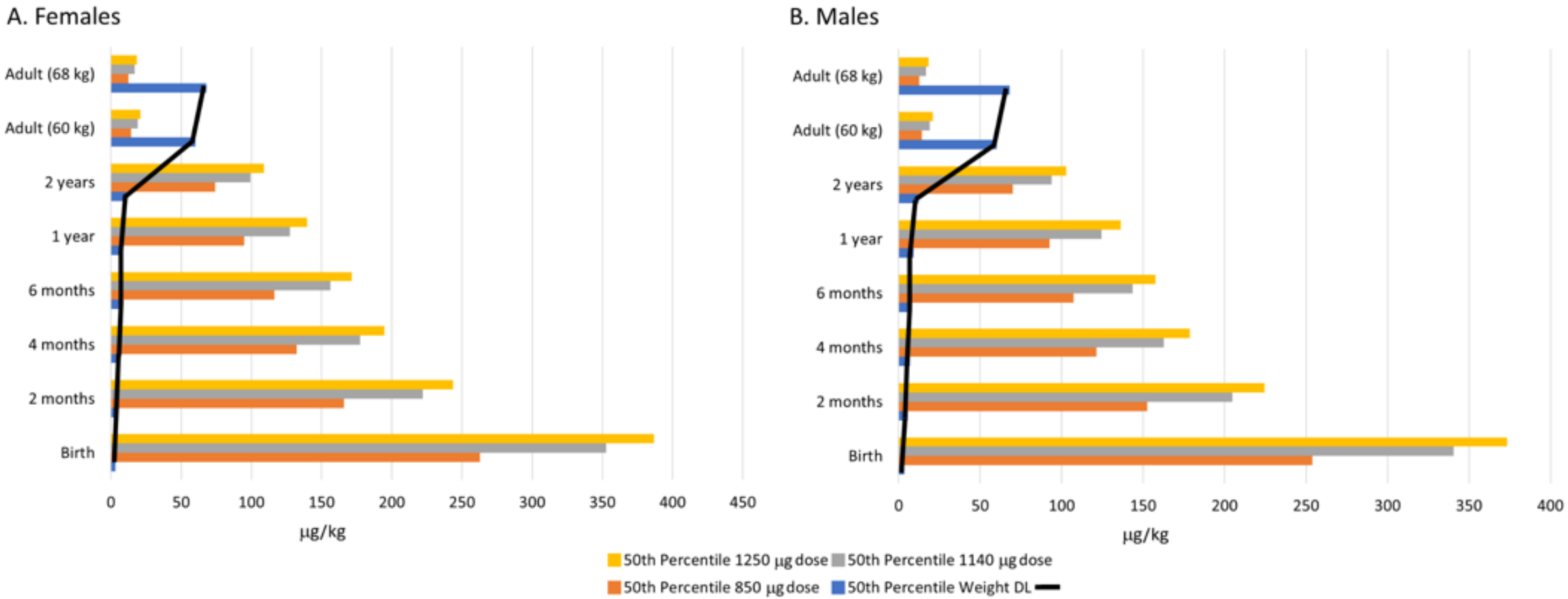
aluminum. Two studies were identified that provided sufficient information on the levels of aluminum in the basal diet. McCormack et al. (1979) and Domingo et al. (1989) did not find any significant alterations in pup viability/lethality, pup body weight, or the incidence of malformation in rats exposed to 110 mg Al/kg/day as aluminum chloride in the diet on gestation days 6–19 (McCormack et al. 1979) or 141 mg Al/kg/day as aluminum nitrate administered via gavage on gestation days 6–15 (Domingo et al. 1989). Neither study evaluated the potential neurotoxicity of aluminum following acute-duration exposure; intermediate-duration studies provide strong evidence that the nervous system (in adults and developing organisms) is the most sensitive target of aluminum toxicity.

- An MRL of 1 mg Al/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to aluminum.

A fair number of animal studies have examined the oral toxicity of aluminum following intermediate-duration exposure. A subset of these studies that provide information on the aluminum content of the basal diet and involved ex[illegible] the focus of this discussion. With the possible exception of reproductive function, these studies have examined most

Problems with Aluminum Dosing in Vaccines

- “Limits” from FDA are expressed as mcg per dose, not mg/kg/day
- Amounts are based on efficacy, not dose escalation safety studies from injections in age-relevant animals
- Dose exposure from >1 vaccine per day is not regulated and FDA has provided no guidance on per day limits

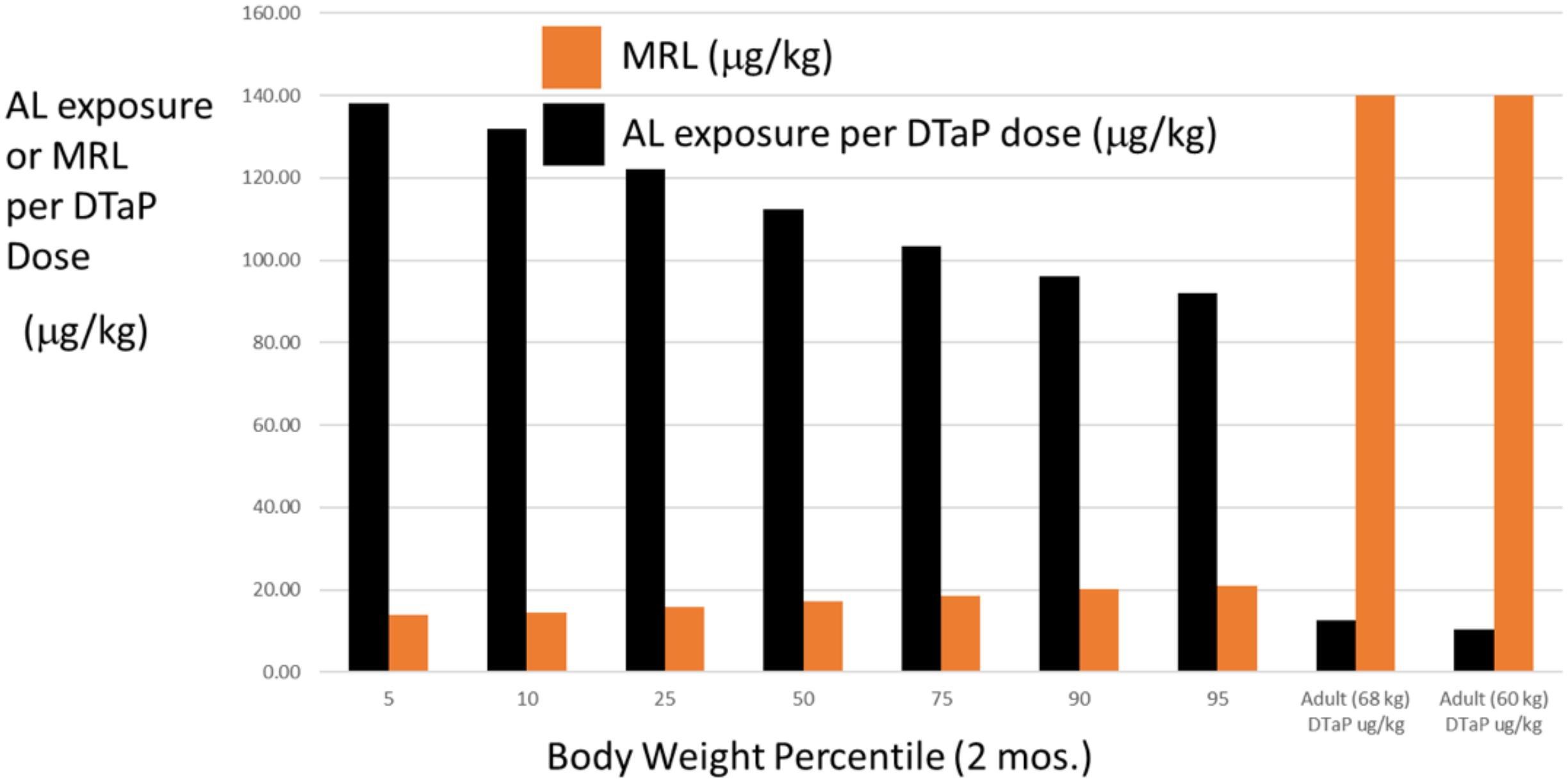


Toxicology

Reconsideration of the immunotherapeutic pediatric safe dose levels of aluminum

James Lyons-Weiler[a,*], Robert Ricketson[b]

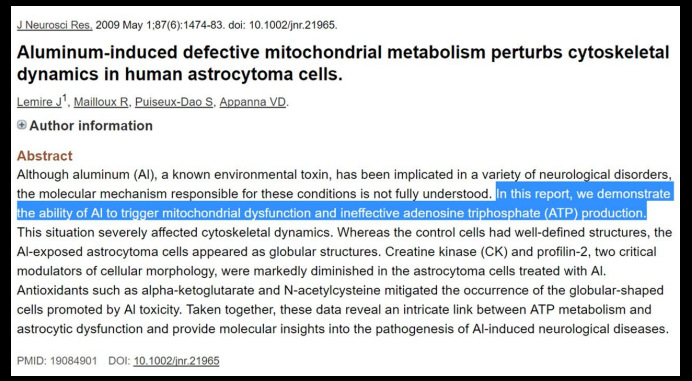
[a] Institute for Pure and Applied Knowledge, 2912 Kilcairn Lane, Allison, PA 15101, United States


AL exposure or MRL per DTaP Dose
(µg/kg)
160.00
140.00
120.00
100.00
80.00
60.00
40.00
20.00
0.00
MRL (µg/kg)
AL exposure per DTaP dose (µg/kg)
5
10
25
50
75
90
95
Adult (68 kg) DTaP ug/kg
Adult (60 kg) DTaP ug/kg
Body Weight Percentile (2 mos.)

How is Aluminum Neuro- and Immunotoxic?

- Accumulates in brain tissue
- Amyloid is part aluminum
- Direct mitotoxicity
- Cytoskeletal dynamics in astroctyes

- Endoplasmic reticulum stress (ER Stress)



J Neurosci Res. 2009 May 1;87(6):1474-83. doi: 10.1002/jnr.21965.

Aluminum-induced defective mitochondrial metabolism perturbs cytoskeletal dynamics in human astrocytoma cells.

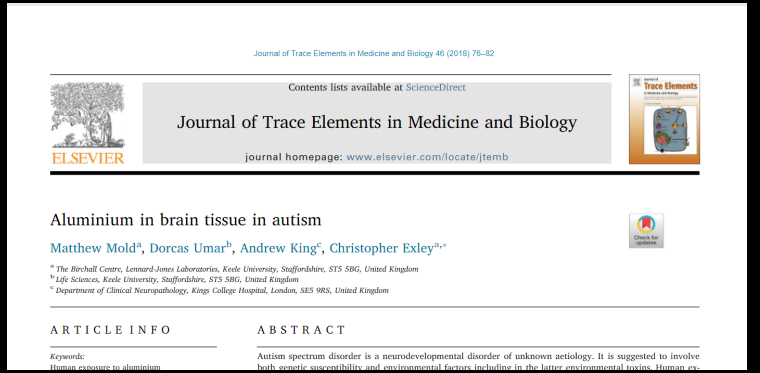
Lemire J[1], Mailloux R, Puiseux-Dao S, Appanna VD.

Author information

Abstract

Although aluminum (Al), a known environmental toxin, has been implicated in a variety of neurological disorders, the molecular mechanism responsible for these conditions is not fully understood. In this report, we demonstrate the ability of Al to trigger mitochondrial dysfunction and ineffective adenosine triphosphate (ATP) production. This situation severely affected cytoskeletal dynamics. Whereas the control cells had well-defined structures, the Al-exposed astrocytoma cells appeared as globular structures. Creatine kinase (CK) and profilin-2, two critical modulators of cellular morphology, were markedly diminished in the astrocytoma cells treated with Al. Antioxidants such as alpha-ketoglutarate and N-acetylcysteine mitigated the occurrence of the globular-shaped cells promoted by Al toxicity. Taken together, these data reveal an intricate link between ATP metabolism and astrocytic dysfunction and provide molecular insights into the pathogenesis of Al-induced neurological diseases.

PMID: 19084901 DOI: 10.1002/jnr.21965



Journal of Trace Elements in Medicine and Biology 46 (2018) 76–82

Contents lists available at ScienceDirect

Journal of Trace Elements in Medicine and Biology

journal homepage: www.elsevier.com/locate/jtemb

ELSEVIER

Aluminium in brain tissue in autism

Matthew Mold[a], Dorcas Umar[b], Andrew King[c], Christopher Exley[a,*]

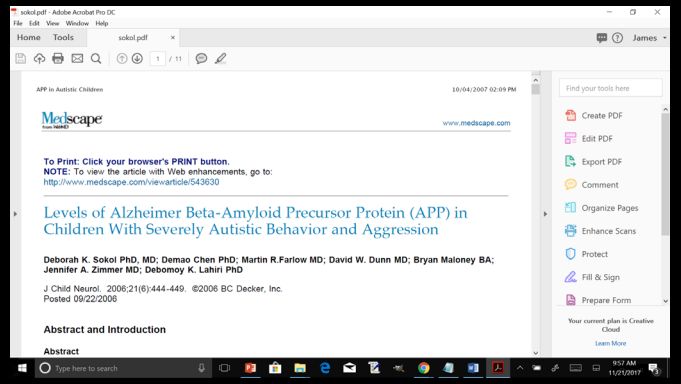
[a] The Birchall Centre, Lennard-Jones Laboratories, Keele University, Staffordshire, ST5 5BG, United Kingdom
[b] Life Sciences, Keele University, Staffordshire, ST5 5BG, United Kingdom
[c] Department of Clinical Neuropathology, Kings College Hospital, London, SE5 9RS, United Kingdom

ARTICLE INFO

Keywords:
Human exposure to aluminium

ABSTRACT

Autism spectrum disorder is a neurodevelopmental disorder of unknown aetiology. It is suggested to involve both genetic susceptibility and environmental factors including in the latter environmental toxins. Human ex-



sokol.pdf - Adobe Acrobat Pro DC

File Edit View Window Help

Home Tools sokol.pdf James

APP in Autistic Children 10/04/2007 02:09 PM

Medscape www.medscape.com

To Print: Click your browser's PRINT button.
NOTE: To view the article with Web enhancements, go to:
http://www.medscape.com/viewarticle/543630

Levels of Alzheimer Beta-Amyloid Precursor Protein (APP) in Children With Severely Autistic Behavior and Aggression

Deborah K. Sokol PhD, MD; Demao Chen PhD; Martin R.Farlow MD; David W. Dunn MD; Bryan Maloney BA; Jennifer A. Zimmer MD; Debomoy K. Lahiri PhD

J Child Neurol. 2006;21(6):444-449. ©2006 BC Decker, Inc.
Posted 09/22/2006

Abstract and Introduction

Abstract

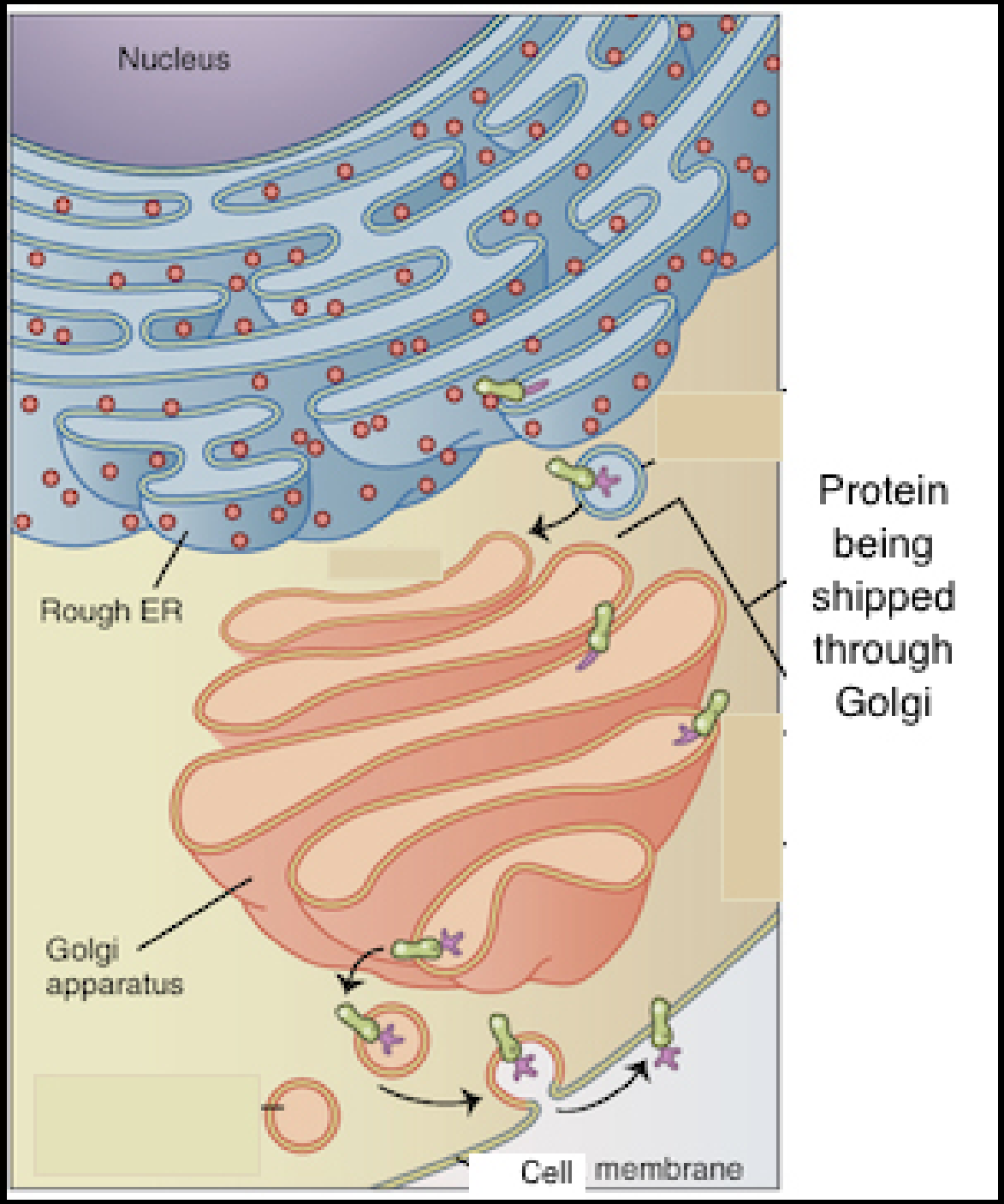
Find your tools here

Create PDF
Edit PDF
Export PDF
Comment
Organize Pages
Enhance Scans
Protect
Fill & Sign
Prepare Form

Your current plan is Creative Cloud
Learn More

Type here to search 9:57 AM 11/21/2017

ER Stress


Nucleus
Rough ER
Protein being shipped through Golgi
Golgi apparatus
Cell membrane

MBP - Myelin basic prote

Secure | https://www.uniprot.org/uniprot/P02686

Apps | Studies that the CDC | www.scifedpublisher | www.pinellaschat.co | JACK LIST - Google | Dr. Patricia Kane, PhD | Aluminium Toxicity | Nudge or Grudge?

ewer

able

All None

& Taxonomy

lar location

gy & Biotech

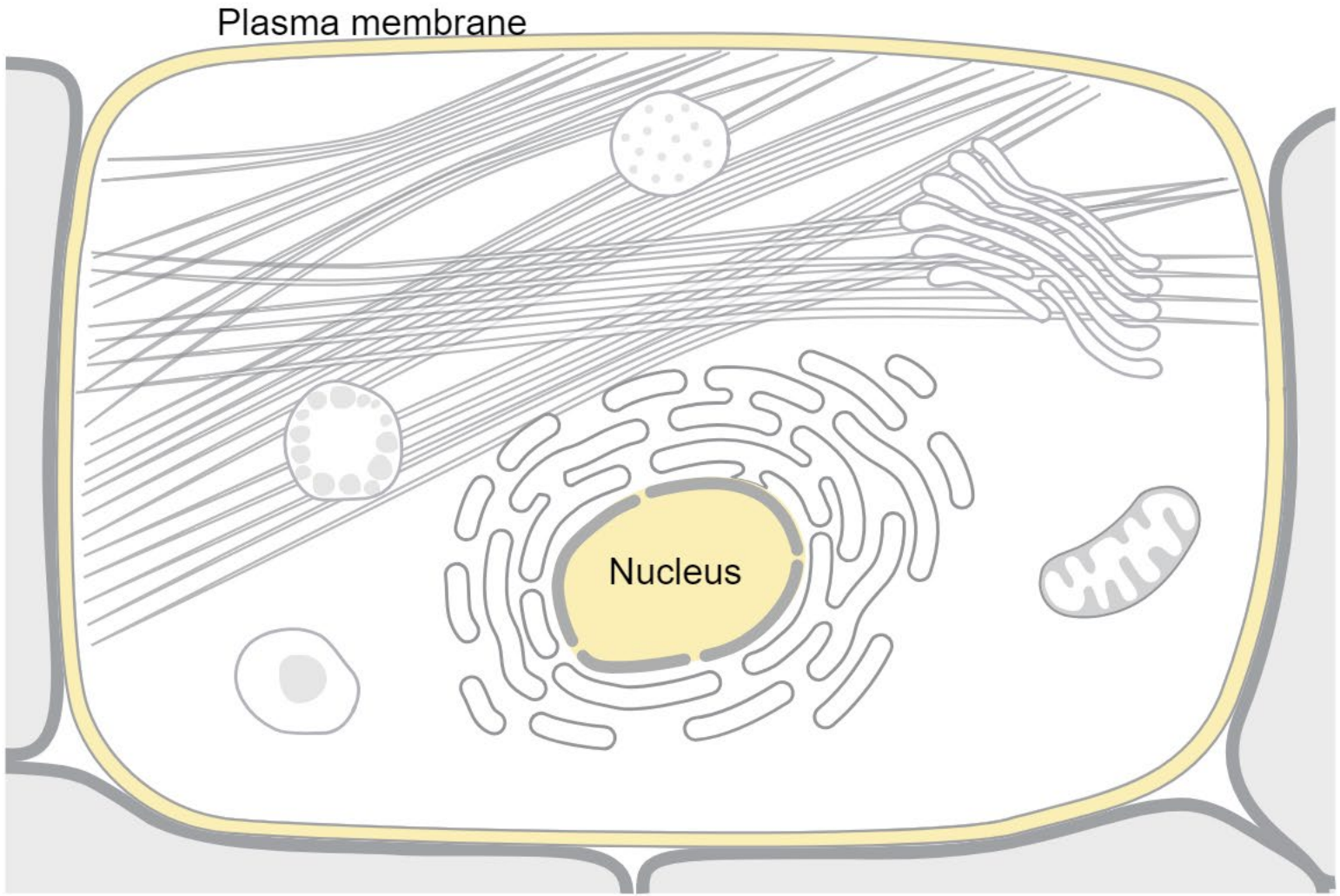
rocessing

ion

on

e

& Domains



Graphics by Christian Stolte; Source: COMPARTMENTS

Plasma membrane

Myelin membrane

Cytoplasmic side

Note: Cytoplasmic s

Isoform 3 :

Nucleus

Nucleus 1

Note: Targeted to nu

Manual annotation | Automatic computational assertion

Type here to search

3:41 PM
5/29/2018

New IPAK Research – 2018

Autism-Open Access

ISSN: 2165-7890

James Lyons-Weiler, Autism-Open Access 2018, 8:1
DOI: 10.4172/2165-7890.1000224

Review Article Open Access

Autism is an Acquired Cellular Detoxification Deficiency Syndrome with Heterogeneous Genetic Predisposition

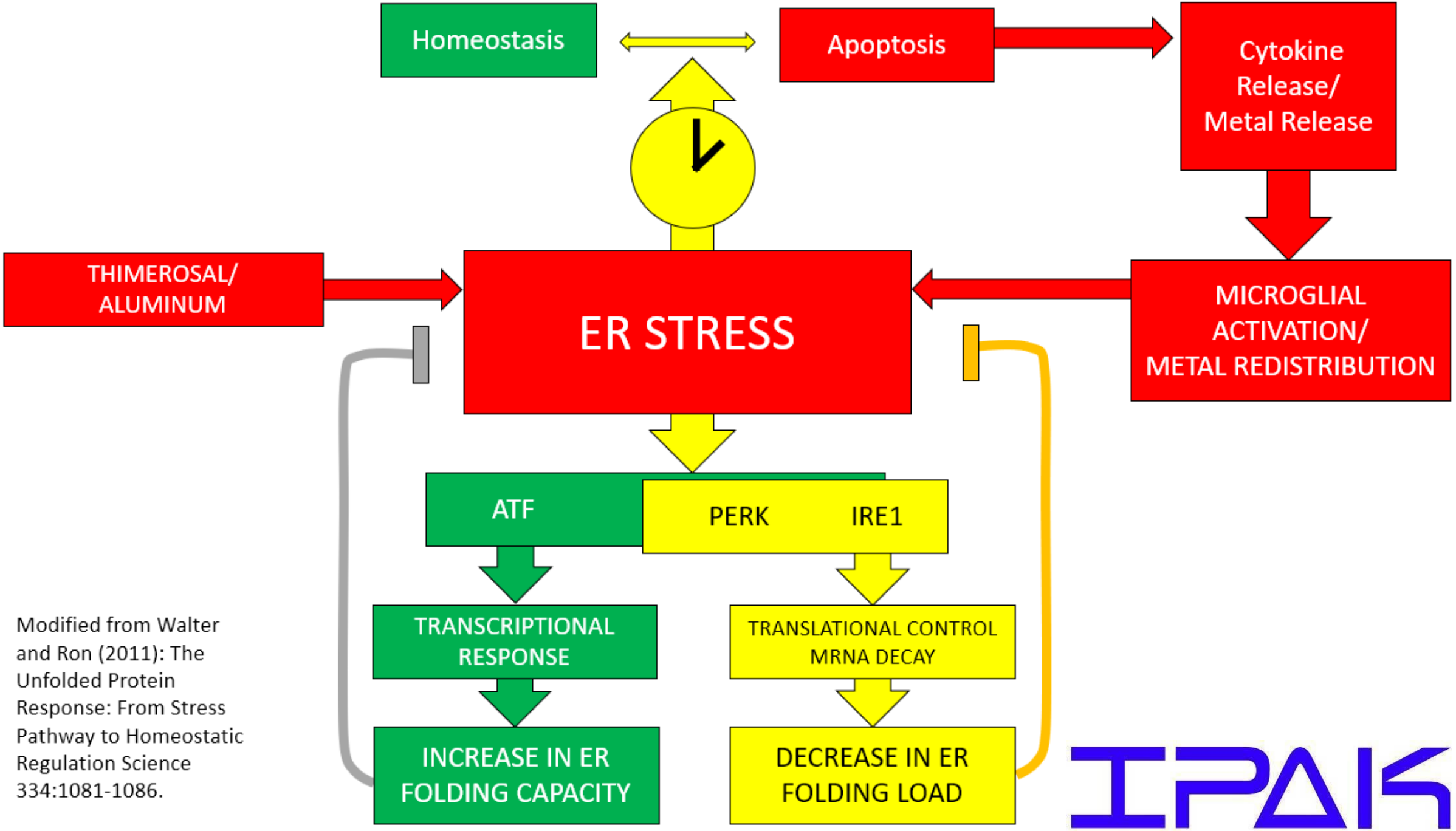
James Lyons-Weiler*

The Institute for Pure and Applied Knowledge, Pittsburgh, PA, USA

***Corresponding author:** James Lyons-Weiler, The Institute for Pure and Applied Knowledge, Pittsburgh, USA, Tel: 4127288743; E-mail: jim@ipaknowledge.org

Received date: January 19, 2018; **Accepted date:** January 26, 2018; **Published date:** March 16, 2018

Abstract

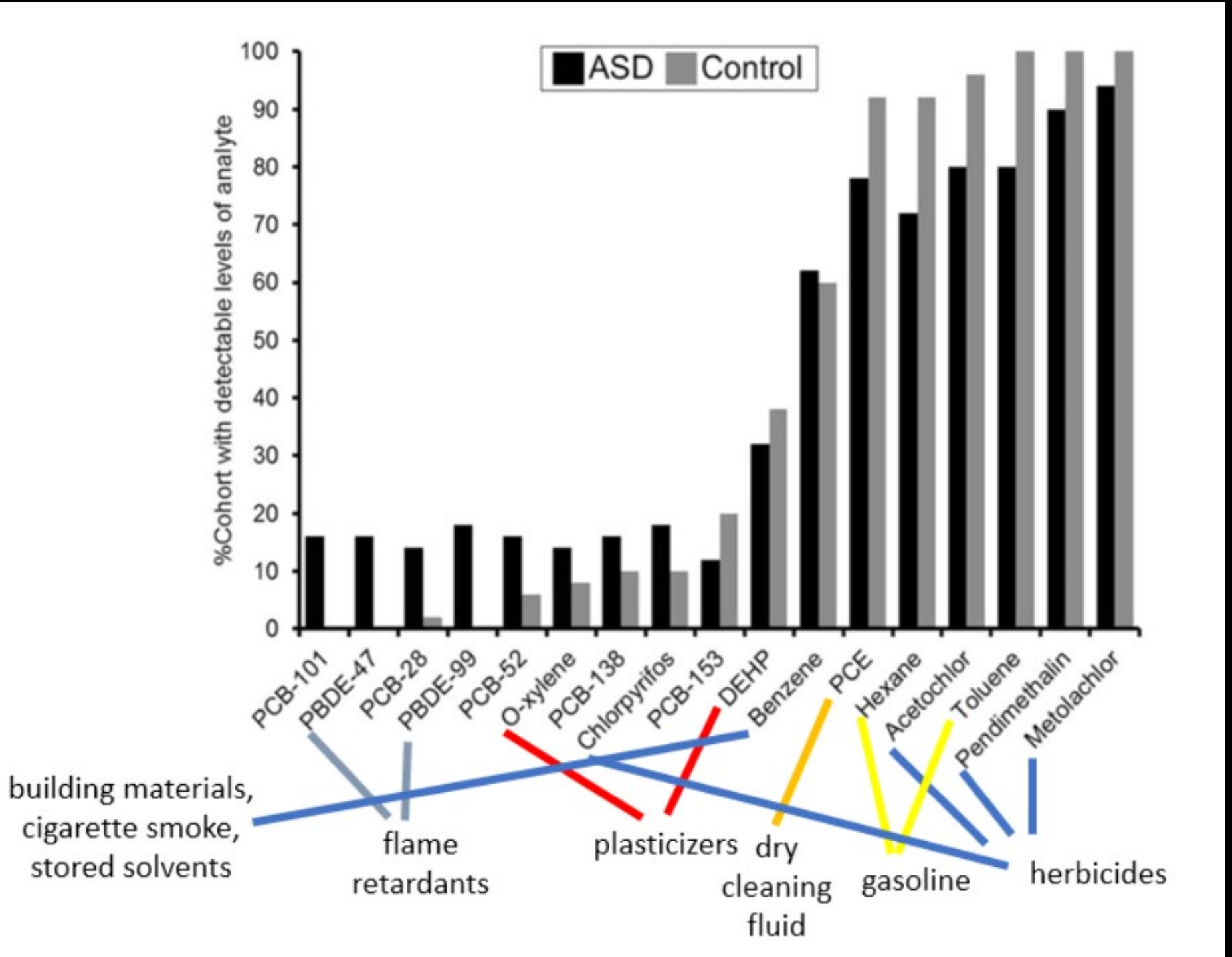


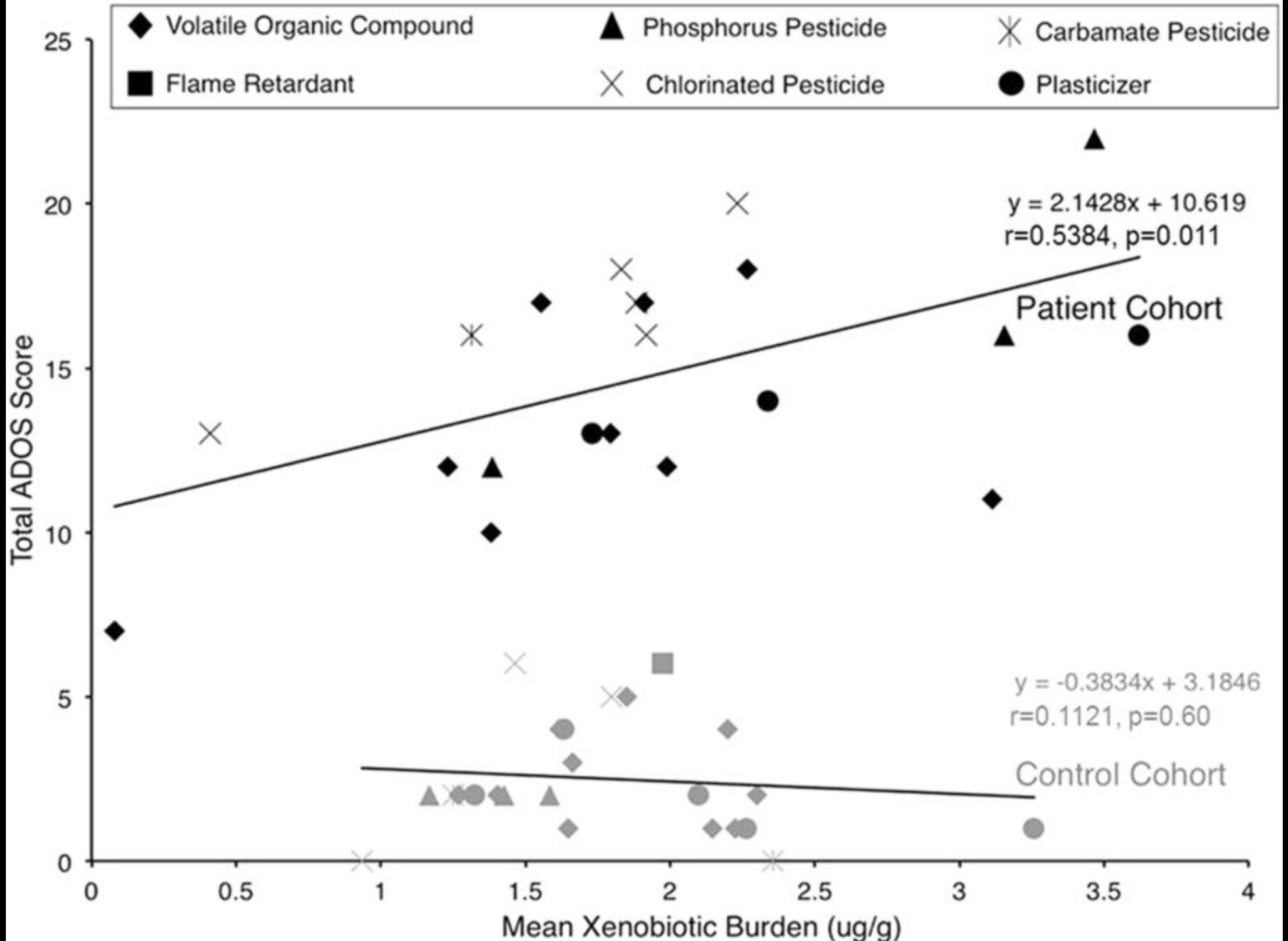
Modified from Walter and Ron (2011): The Unfolded Protein Response: From Stress Pathway to Homeostatic Regulation Science 334:1081-1086.

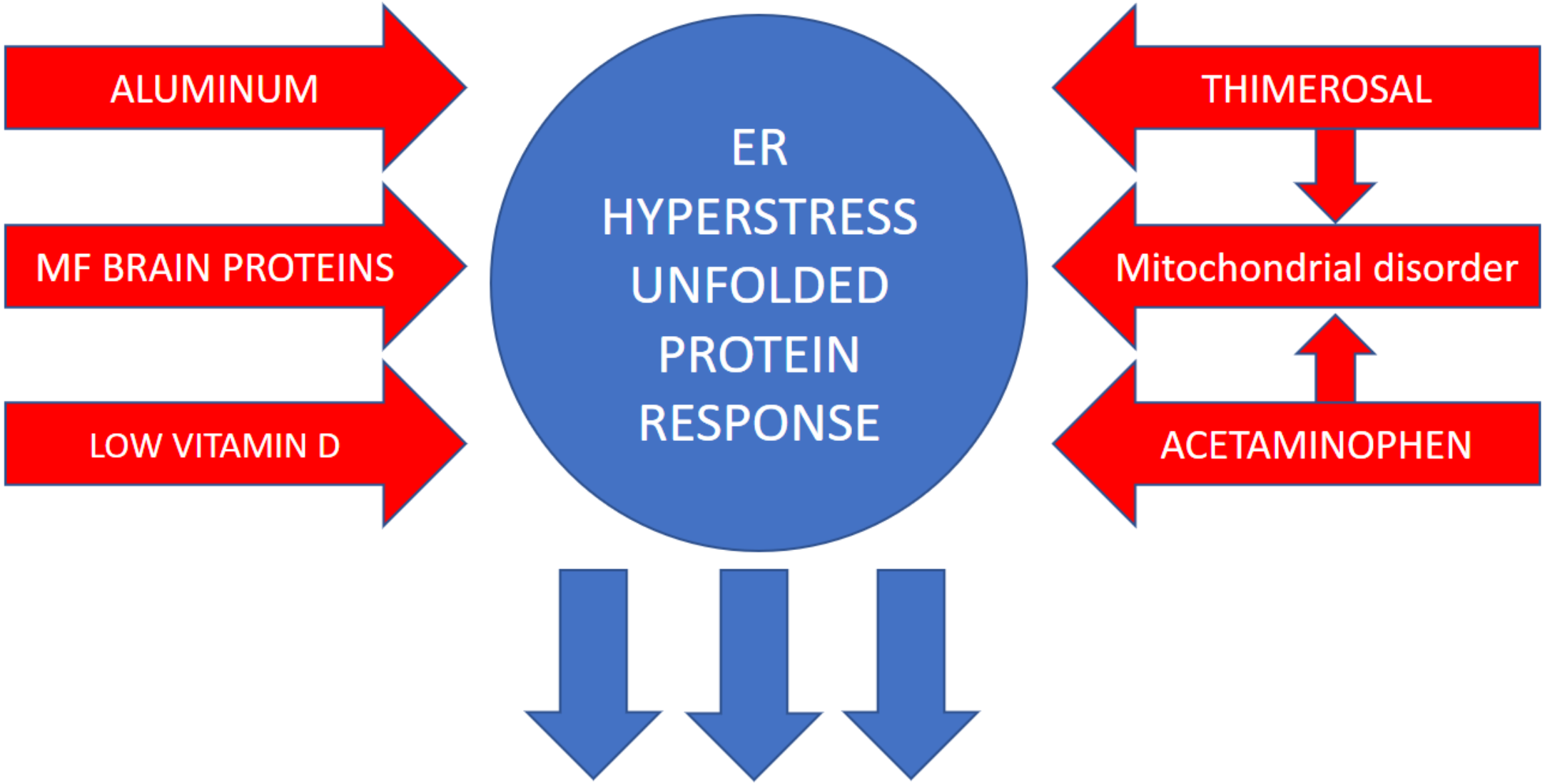
Golgi Genes Associated w/ASD	Citation
REEP3	Castermans et al. (2007) [72]
C3ORF58	Dudkiewicz et al. (2013) [73]
SLC35A3	Edvarson et al. (2013) [74]
Neurobeachin	Niesmann et al. (2011);Nuytens et al. (2013);Volders et al. (2013) [77]
KIRREL3	Liu et al. (2015) [75]
VPS13B	Rejeb et al. (2017) [78]
TRAPPC6B	Marin-Valencia (2018) [76]
ER and UPR-Inducing Genes Associated w/ASD	**Citation**
RELN	Lammert et al. (2017) [79]
Neuroligin1	Tristan-Clavijo et al. (2015) [81]
Neuroligin2	Tu et al. (2017) [80]
Neuroligin3	Ulbrich et al. (2016) [23]
Neuroligin4	Zhang et al. (2009) [82]
GPR37	Tanabe et al. (2015) [119]
GPR85	Fujita-Jimbo (2015) [84]
RAB39B	Mignona et al. (2015) [83]
NHE6	Illie et al. (2014) [65]
Tuberin	Reith et al. (2011) [109]
CNTNAP	Momoi et al. (2009) [30]
CNTNAP2	Falivelli et al. (2012) [86]
CADM1	Fujita et al. (2010) [88]; Momoi et al. (2009) [30]

What the ER Hyperstress Model Explains in ASD

- How AL adjuvants work (apoptosis -> cytokine release)
- Why there are so many genes involved in ASD risk (>850)
- Why many ASD kids have multiple chemical sensitivity
- Why kids w/ASD accumulate toxins
- Why some kids develop ASD after vaccination, and some do not
- Why kids w/ASD have high amounts of oddly folded proteins in their blood
- How Thimerosal and Aluminum toxicity can multiply risk
- Why multiple AL vaccines at once increases risk of morbidity and mortality


ASD
Control
%Cohort with detectable levels of analyte
100
90
80
70
60
50
40
30
20
10
0
PCB-101
PBDE-47
PCB-28
PBDE-99
PCB-52
O-xylene
PCB-138
Chlorpyrifos
PCB-153
DEHP
Benzene
PCE
Hexane
Acetochlor
Toluene
Pendimethalin
Metolachlor
building materials, cigarette smoke, stored solvents
flame retardants
plasticizers
dry cleaning fluid
gasoline
herbicides


Volatile Organic Compound
Phosphorus Pesticide
Carbamate Pesticide
Flame Retardant
Chlorinated Pesticide
Plasticizer
y = 2.1428x + 10.619
r=0.5384, p=0.011
Patient Cohort
y = -0.3834x + 3.1846
r=0.1121, p=0.60
Control Cohort
Total ADOS Score
Mean Xenobiotic Burden (ug/g)
0
5
10
15
20
25
0
0.5
1
1.5
2
2.5
3
3.5
4

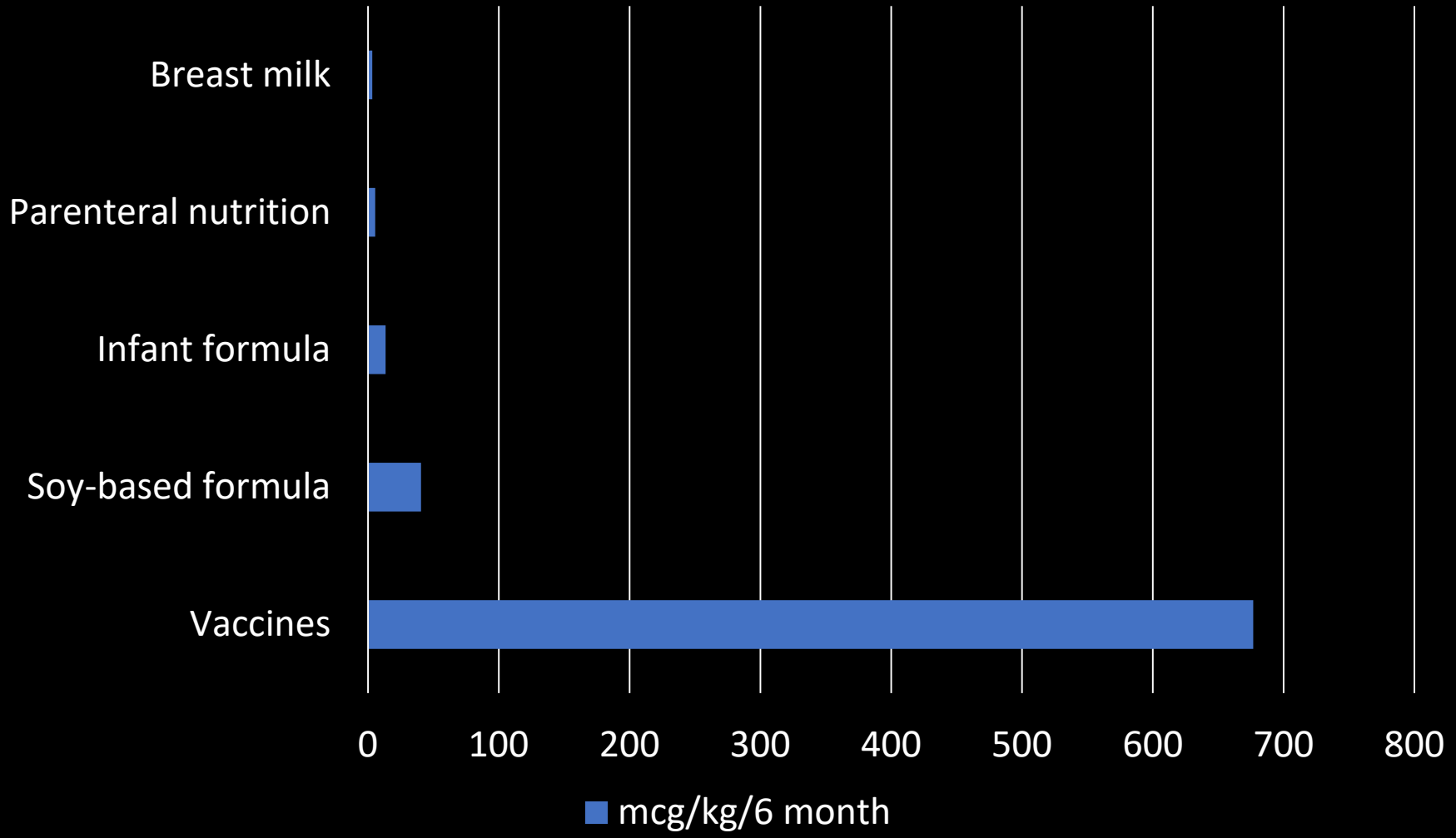


apoptosis, cytokine release, metals re-distribution,
chronic microglial activation, aberrant pruning,
E/I ratio skew, ASD, ADHD, other NDD

IPAK

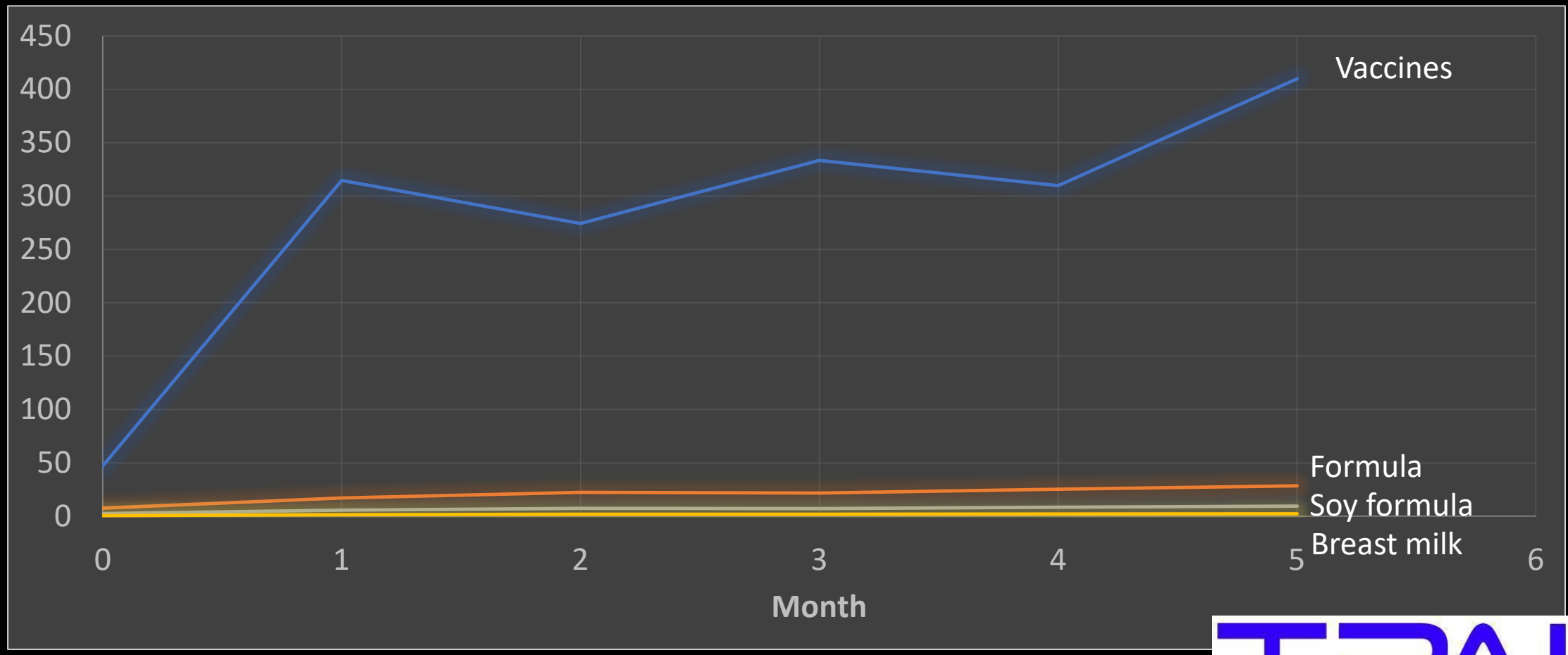
FDA's Claim: More from Diet Than Vaccines

Total Exposure in Newborns 0-6 mos

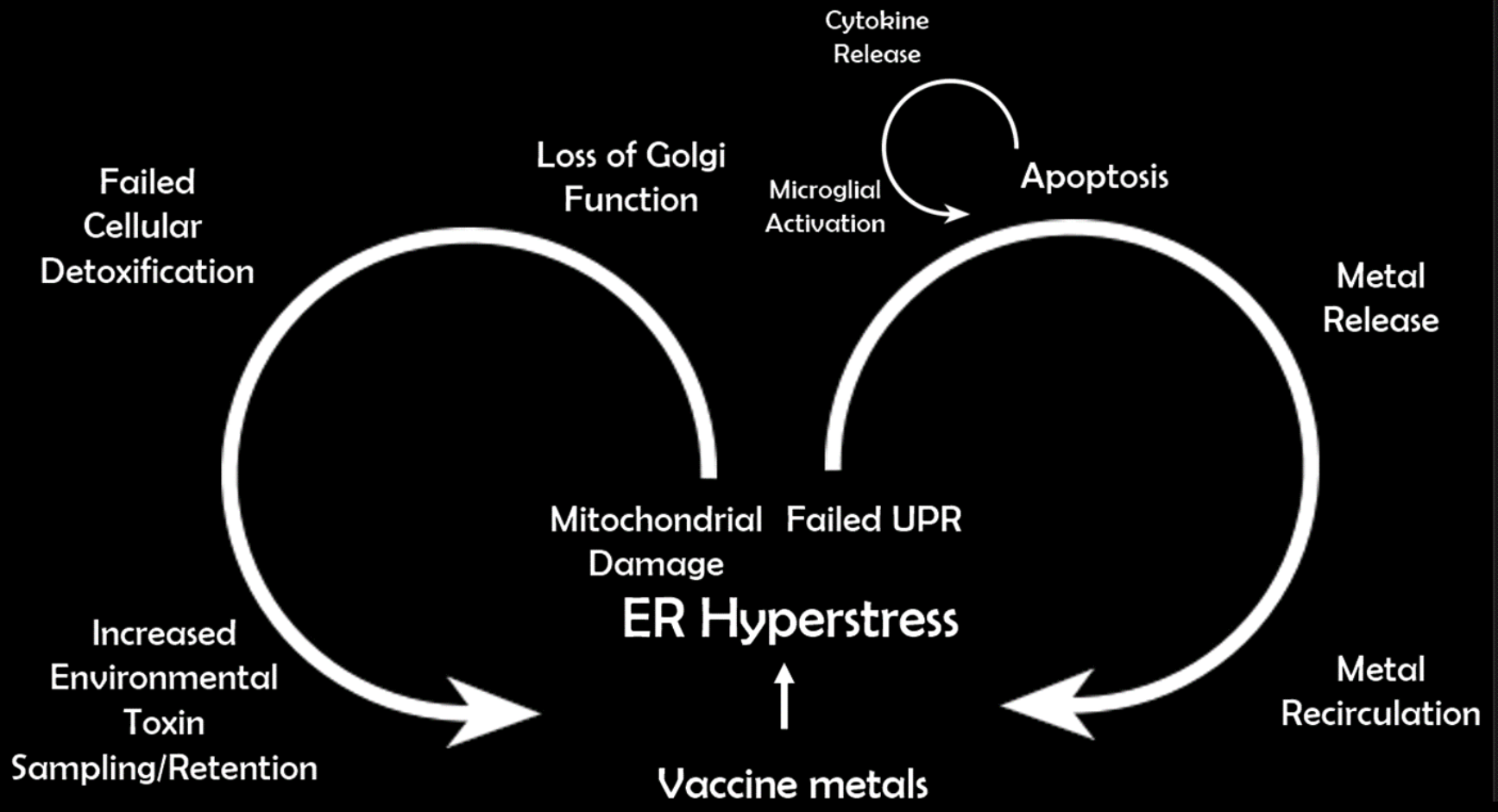


FDA's Claim: More from Diet Than Vaccines

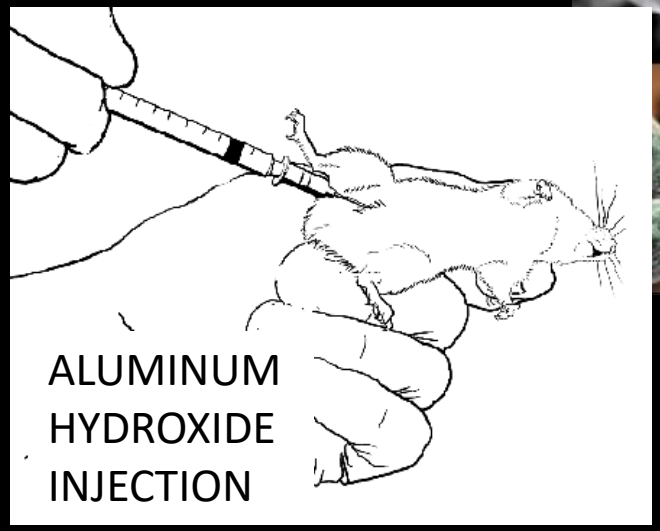
Assuming clearance rates from Flarend et al (5.6%/28 days)

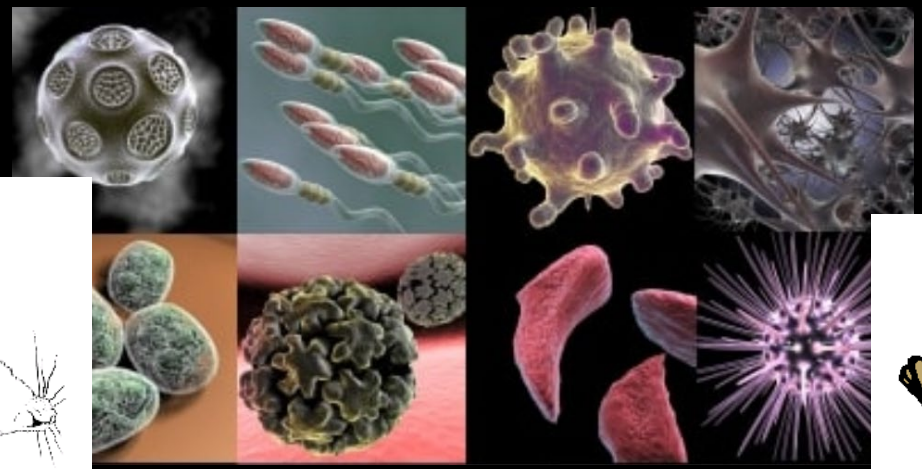


Part 2 Autoimmunity from ER Hyperstress



Animal Models of Autoimmunity





ANTIGEN
EXPOSURE

- Allergic rhinitis
- Arthritis
- Athlerosclerosis
- Antiphospholipid syndrome (APS)
- Asthma
- Food allergies
- Gastrointestinal allergy
- Glomerulonephritis
- Lupus
- Sjögren's syndrome

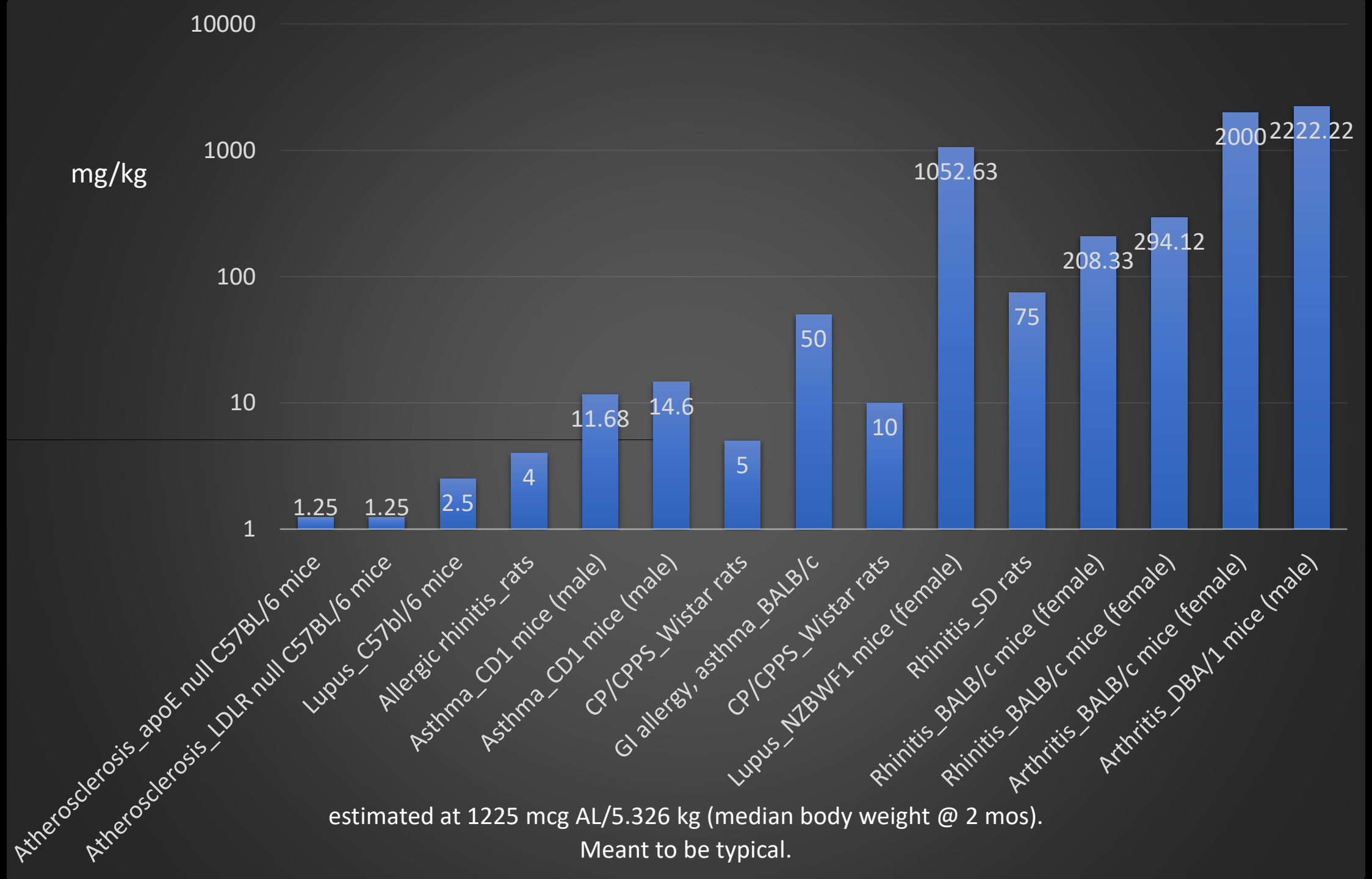
AA Disease	Aluminum Type	Symptom Manifestations	Citation
allergic asthma	Al(OH)3	asthma	Elsakkar et al., 2016 [40]
	Al(OH)3		Bibi et al., 2014 [75]
allergic rhinitis	Al(OH)3	allergic rhinitis immune suppression	Xi et al., 2014 [45]
	Al(OH)3	allergic rhinitis	Li and Geng, 2015 [66]
	Al(OH)3	allergic rhinitis	Yasar et al., 2016[39]
	Al(OH)3	allergic rhinitis	Yang et al., 2016[44]
bronchial asthma	Al(OH)3	bronchial asthma	
antiphospholipid syndrome	alhydrogel	APS antibodies	Zivković et al., 2013[80]
		Al(OH)3	Zivkovic et al., 2011[81]
arthritis	Al(OH)3	collagen-induced arthritis	Sagawa et al., 2005[46]
	Al(OH)3	severe destructive Lyme arthritis	Croke et al., 2000 [88]

atherosclerosis	Al(OH)3	OVA-specific IgG/ chymase increase	Nishizono et al. 1999 [101]
	Al(OH)3	atherosclerotic lesions	Zhu et al. 2014[37]
chronic prostatitis/ chronic pelvic pain syndrome	Al(OH)3	increased TNF-α and IgG prostatitis	Qi et al., 2012
gastrointestinal allergy preceding asthma	aluminum potassium sulfate	pulmonary inflammation	Brandt et al., 2006 [42]
systemic lupus erythematosus	Al(OH)3	kidney tissue damage decreased RBCs memory deficits brain gliosis	Agmon-Levin et al., 2014 [43]
	Al(OH)3	DC and lymphocyte activation and Sm/RNP autoantigen	Kelly-Scumpia et al., 2007 [38]
	Al(OH)3	accelerate proteinuria weight loss	Favoino et al., 2014 [223]

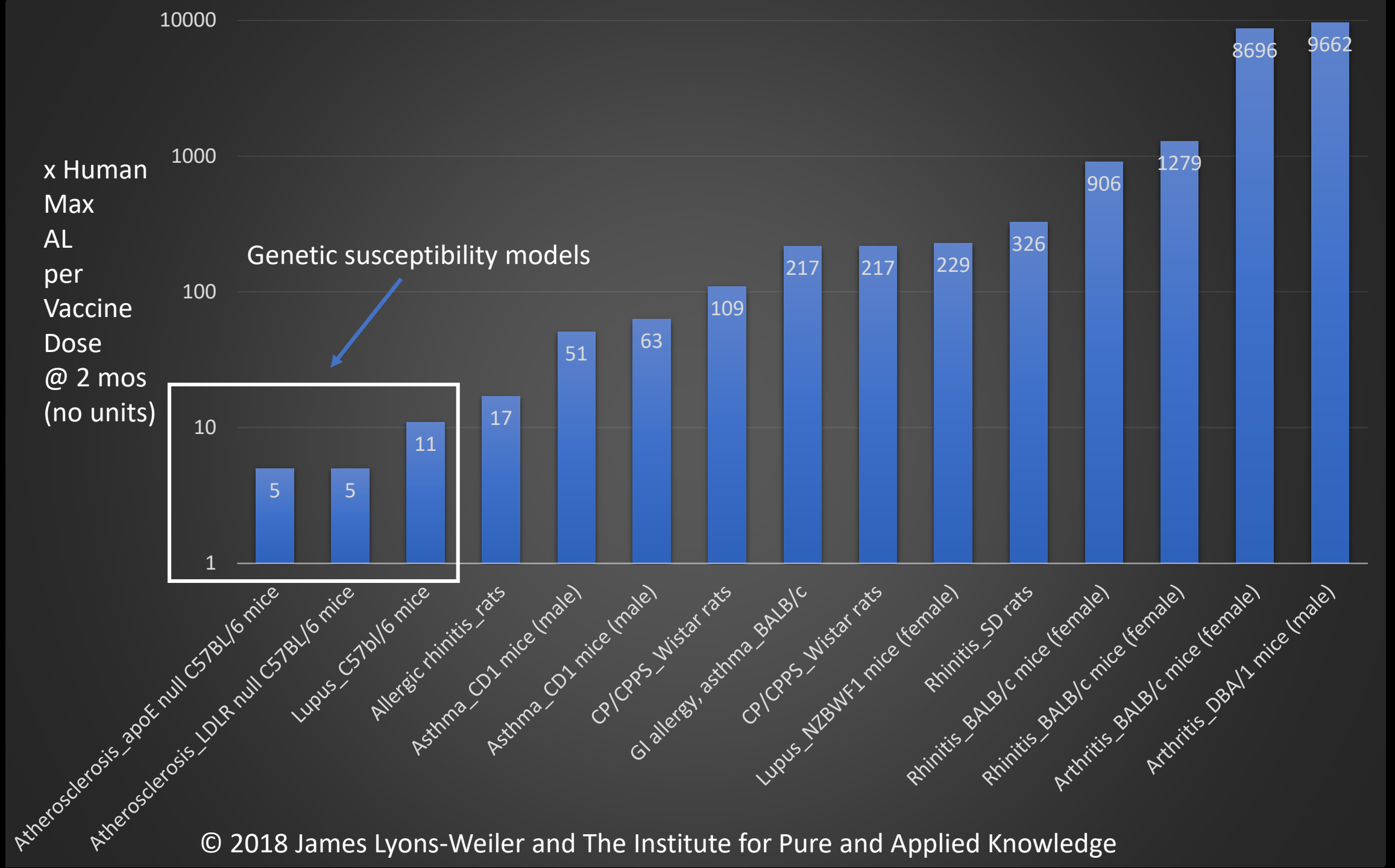
motor neuron disease	Al(OH)3 motor neuron degeneration	motor deficits	Shaw & Petrik, 2009 [224]
Sjögren's Syndrome	Al(OH)3 dysfunction	salivary gland	Bagavant et al., 2014 [113]
food allergy	Al(OH)3	IG-E peanut allergy	Shishehbor et al., 2010 [118]
	Al(OH)3	soy, peanut, pea, apple, ovalbumin	Ahrens et al., 2014 [119]
	multiple vaccines allergies	peanut and egg	Hoyt et al., 2015 [120]

How Do Animal Model Doses Compare to Human?

- Injected dosing expressed as mcg/kg
- Animal models mcg/kg / Human doses mcg/kg = no units (1X, 5X, 20X, etc)
- Animal weights were used as reported or estimated from the reported age of animals from suppliers' descriptions
- "Human dose" is the maximum amount expected at 2 mos in the US CDC Schedule (1,225 mcg) for average weight of 5.326 kg @ 2 mos
- This analysis does not consider accumulation
- Not all studies reported mcg amounts



estimated at 1225 mcg AL/5.326 kg (median body weight @ 2 mos).
Meant to be typical.



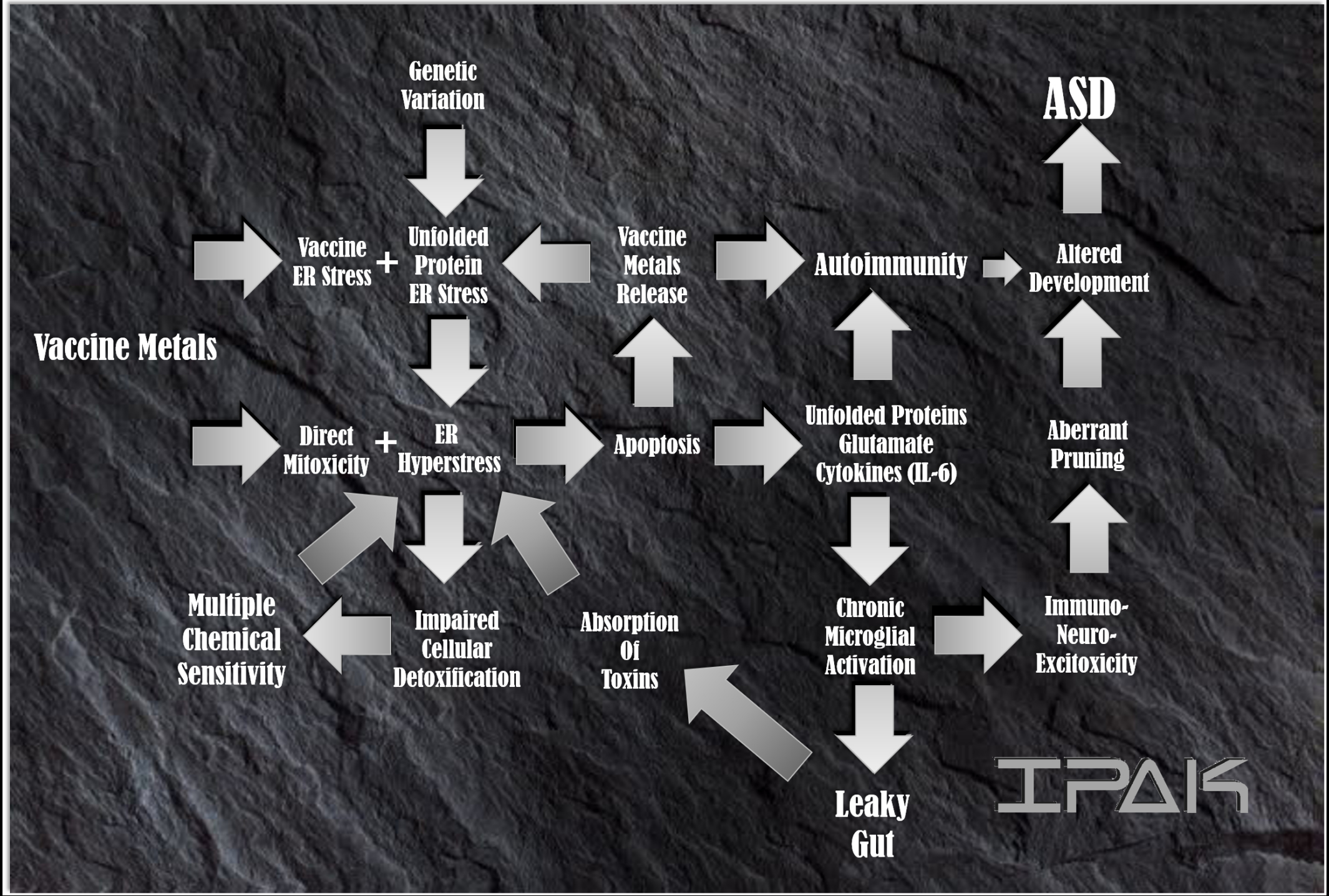
Examples of Unfolded Protein Response/ER Stress in Autoimmune and Autoinflammatory Disorders

Table 3.

Condition	Evidence	Detail	Reference
Amyotrophic Lateral Sclerosis	Review	ER morphology	Jaronen et al, 2014 [148]
		SOD1 accumulation	Doyle et al., 2011 [149]
Gullain-Barre Syndrome	Viral hijack	stress granule protein	Hou et al., 2017 [151]
Rheumatoid Arthritis	anti-citrullinated protein antibodies	GADD34 increased	Clavarino et al. 2016 [152]
		UPR signal	
	haploinsufficiency	GRP78 chaperone	Park et al. 2014 [95]
	immunohistochemistry	GRP78 increased	Dong et al. 2009 [153]
Lupus	gene expression	BLIMP1 UPR	Garaud et al. 2011 [57]

Condition	Adjuvant	Vaccine	Reference
cognitive dysfunction	Al(OH)3	various	Couette et al., 2009[164]
	Al(OH)3		Levart, 2013[165]
	Al(OH)3	vaccines	Bassi et al., 2012[131]
Guillain-Barré Syndrome	Al(OH)3	HepB	Bogdanos et al., 2005[166]
	H1N1		Ahmed et al., 2015[10,163]
Hypoinsulinism (Tissue Scurvy)	Various		Innis, 2013[167]
Rheumatoid arthritis (genetic predisposition)	N/A	H1N1	Basra et al., 2012[168] Ray et al., 2011 (cohort study)[96]
Narcolepsy	N/A	H1N1	Ahmed et al., 2015[10] Verstraeten et al., 2016[169]
vaccine induced immune thrombocytopenic purpura (VI-ITP)	Al(OH)3 n/a	HepB MMR	Meyboom et al., 1995[170] Cecinati et al., 2013[171] O'Leary et al., 2012[172]
vasculitis, death	AAHS	HPV	Tomljenovic and Shaw, 2013[173]

Narcolepsy	N/A	H1N1	Ahmed et al., 2015[10] Verstraeten et al., 2016[169]
vaccine induced immune thrombocytopenic purpura (VI-ITP)	Al(OH)3 n/a	HepB MMR	Meyboom et al., 1995[170] Cecinati et al., 2013[171] O'Leary et al., 2012[172]
vasculitis, death	AAHS	HPV	Tomljenovic and Shaw, 2012[173]
vasculitis	AAHS	HPV	Gomes et al, 2013[174]
thrombocytopenic purpura	AAHS	HPV	Souayah et al. 2011[175] Pugnet et al., 2009[176]
demyelinating disease	AAHS	HPV	Alvarez-Soria et al., 2011[177]
systemic lupus erythematosus	AAHS	HPV	Gatto et al., 2013[163]
premature ovarian failure	AAHS	HPV	Gatto et al., 2013[163]
increased brain AL	AL(OH)3	adjuvant	Redhead et al., 1992[178]
undifferentiated connective tissue disease	AL(OH)3 AL(OH)3	Hepatitis B Hepatitis B	Bruzzese et al., 2013[179] Perricone et al., 2013[162]


Genetic Variation
ASD
Vaccine ER Stress
+
Unfolded Protein ER Stress
Vaccine Metals Release
Autoimmunity
Altered Development
Vaccine Metals
Direct Mitoxicity
+
ER Hyperstress
Apoptosis
Unfolded Proteins Glutamate Cytokines (IL-6)
Aberrant Pruning
Multiple Chemical Sensitivity
Impaired Cellular Detoxification
Absorption Of Toxins
Chronic Microglial Activation
Immuno-Neuro-Excitoxicity
Leaky Gut
IPAK

Policy Analysis: What the FDA Has Said About Aluminum in Vaccines

- *"we have demonstrated that aluminum levels in infants are well below the minimal risk level curves for either median or low-birth weight babies"* – Mitkus et al, 2011 (Vaccine)

- *"When evaluating a vaccine for safety and efficacy, FDA considers adjuvants as a component of the vaccine; they are not licensed separately"* – US FDA Website https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm175909.pdf

- *"An adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety or potency of the product. 21CFR610.15"*

#notonemore