ADJUVANTS in Allergy

MUNICH DE

3RD-5TH JULY 2014

Human Exposure to Aluminium

Christopher Exley PhD

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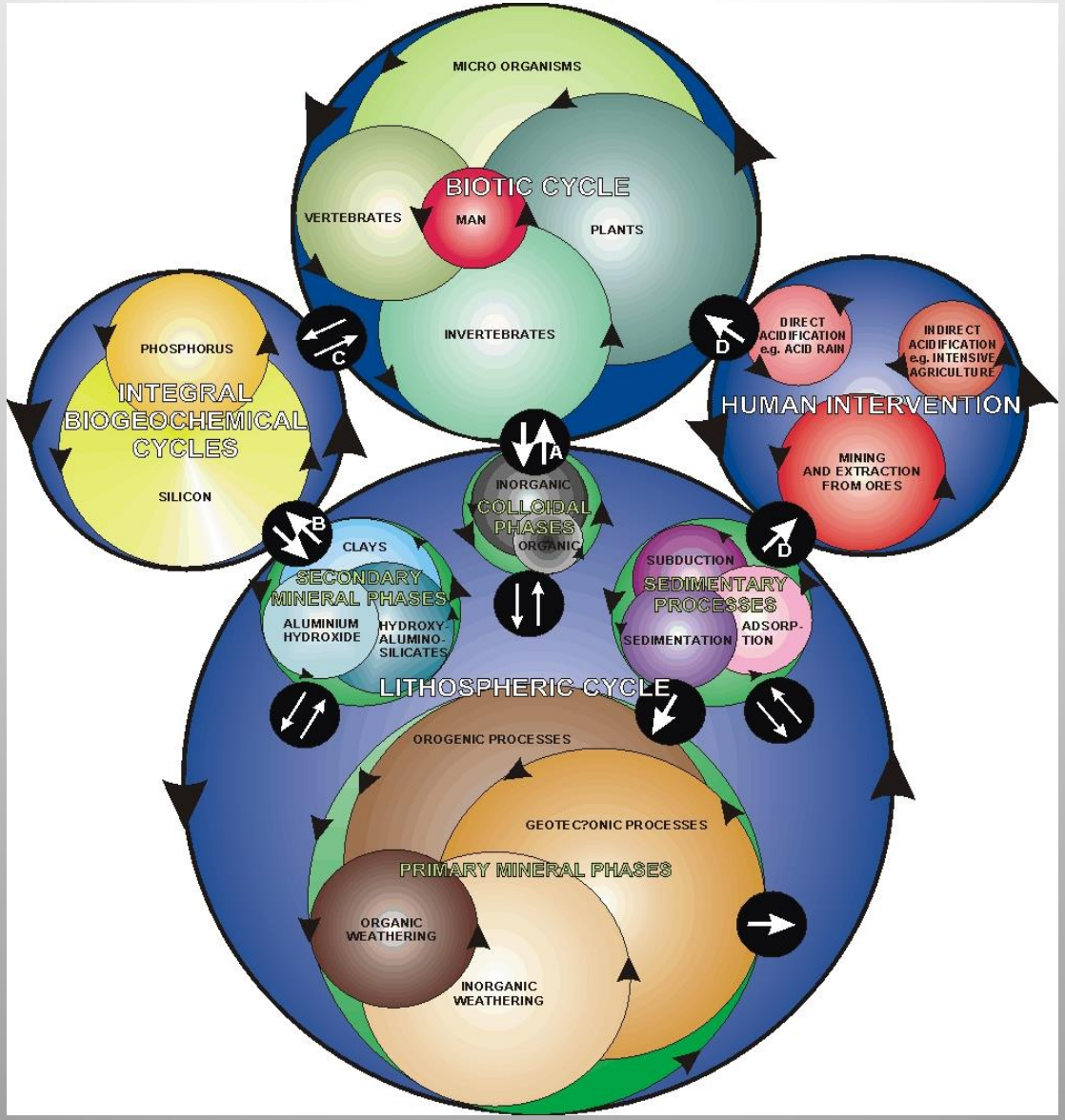
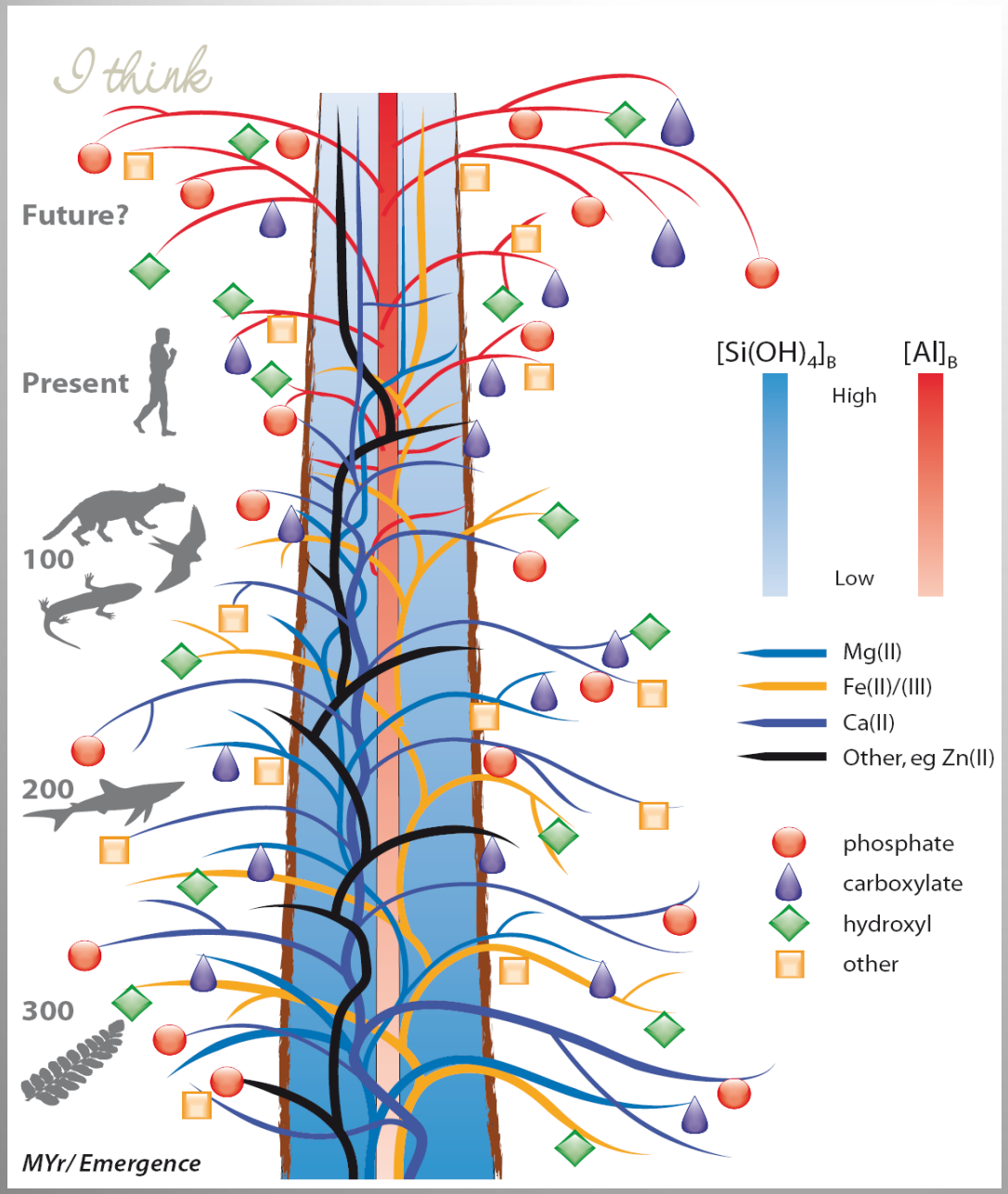
http://www.keele.ac.uk/aluminium/

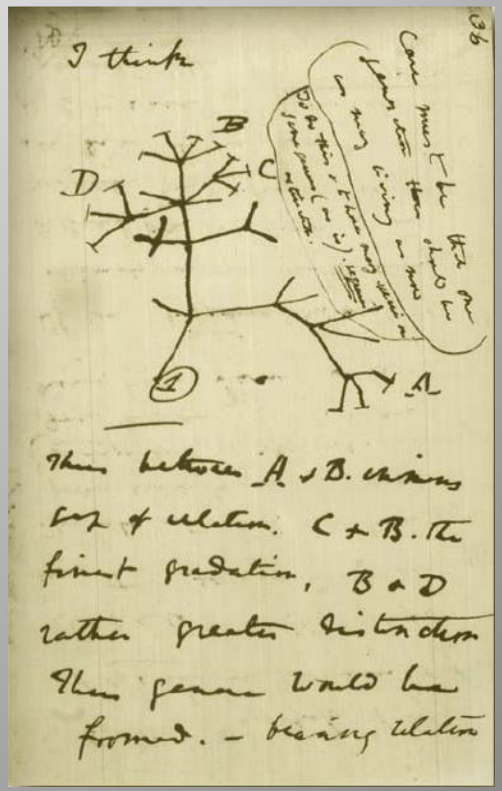


THE BIOGEOCHEMICAL CYCLE OF ALUMINIUM

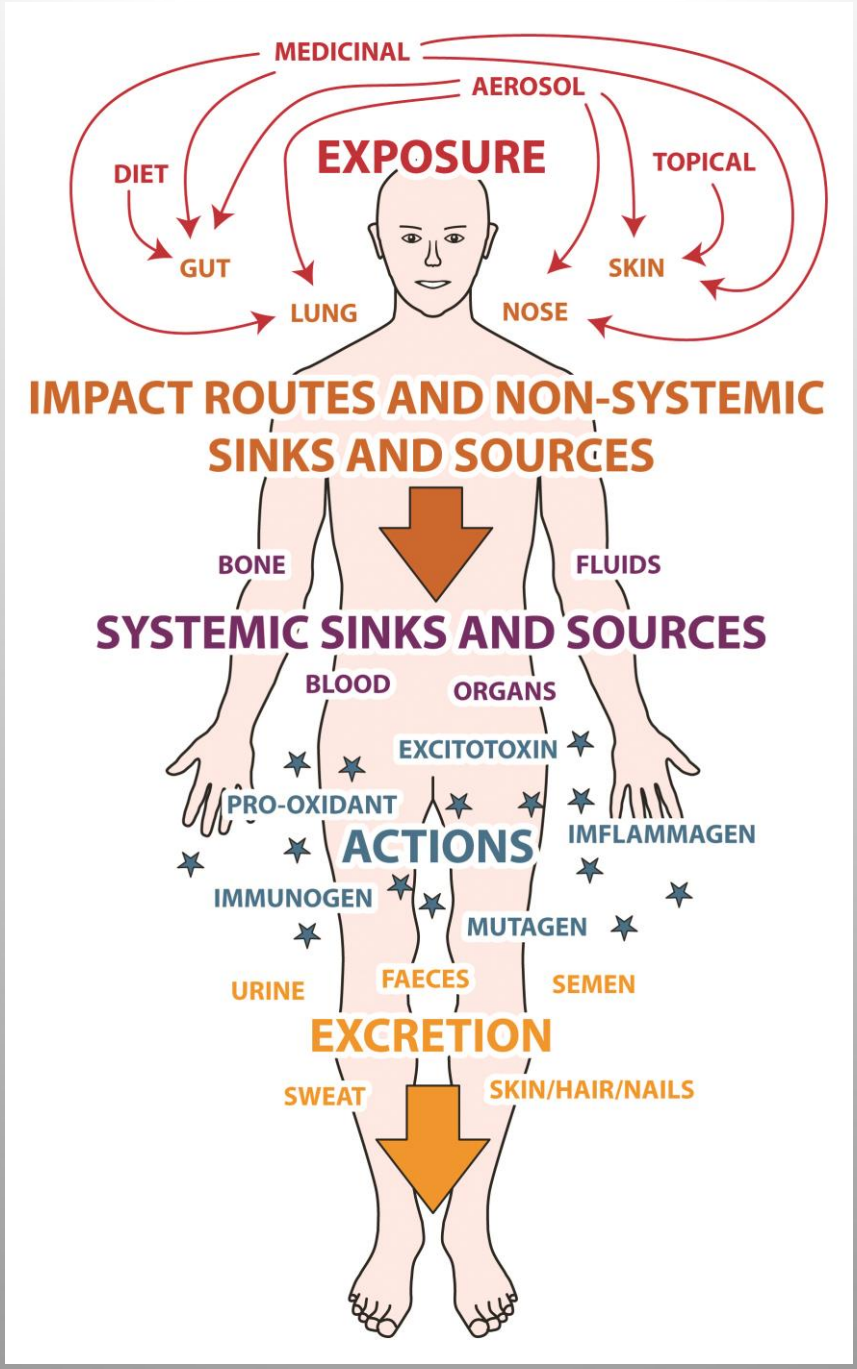
Exley C (2003) A biogeochemical cycle for aluminium ? J. Inorg. Biochem. 97, 1-7.

A Biochemical 'Tree of Life' for the Natural Selection of Aluminium





Exley C (2009) Darwin, natural selection and the biological essentiality of aluminium and silicon. Trends in Biochemical Sciences 34, 589-593.



Exley C (2013) Human exposure to aluminium. Environmental Science:Processes and Impacts 15, 1807-1816.

Elucidating Aluminium's Exposome

Christopher Exley*

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Abstract: The term ***exposome*** has been coined to express the totality of environmental or an environmental exposure (Wild, C.P. *Cancer Epidemiol. Biomarkers Prev.*, **2005** 14, 1847-1850). The biologically non-essential and environmentally ubiquitous element aluminium is arguably the most significant metal toxicant in the lithosphere and it is imperative that its exposome is as fully understood as possible. Identifying the tools required to elucidate and illuminate aluminium's exposome is critical and will help to design and implement current and future experimentation for testing the toxicity of aluminium. It is acknowledged herein that attempts to date to understand the toxicity of aluminium have sometimes suffered from poor experimental design and method but progress has also been stymied by a lack of adequate tools including appropriate computational models. The recent development of a biologically-relevant model of non-equilibrium metal binding should act as a platform for a better understanding of aluminium's exposome.

The biologically-reactive form of Al(III) Al_{BR}

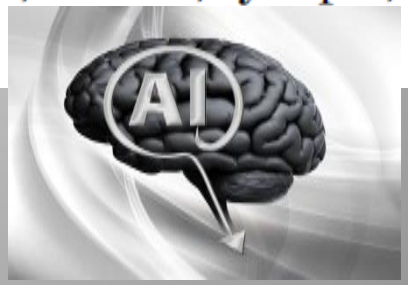
$$Al(H_2O)_6^{3+}{}_{(aq)} \leftrightarrow Al(H_2O)_5OH^{2+}{}_{(aq)} \leftrightarrow Al(H_2O)_4(OH)_2^{+}{}_{(aq)} \leftrightarrow Al(H_2O)_3(OH)_3^{0}{}_{(aq)} \leftrightarrow Al(H_2O)_2(OH)_4^{-}{}_{(aq)} \quad (1)$$

The biological burden of Al (III), Al_{BB}, is the source of biologically-reactive Al(III), Al_{BR}, which when biologically available, Al_{BA}, produces biological effect or toxicity.

$$Al_{BB} \leftrightarrow Al_{BR} \leftrightarrow Al_{BA} \rightarrow \text{Biological Effect / Toxicity} \quad (2)$$

What is 'the body burden' of aluminium?

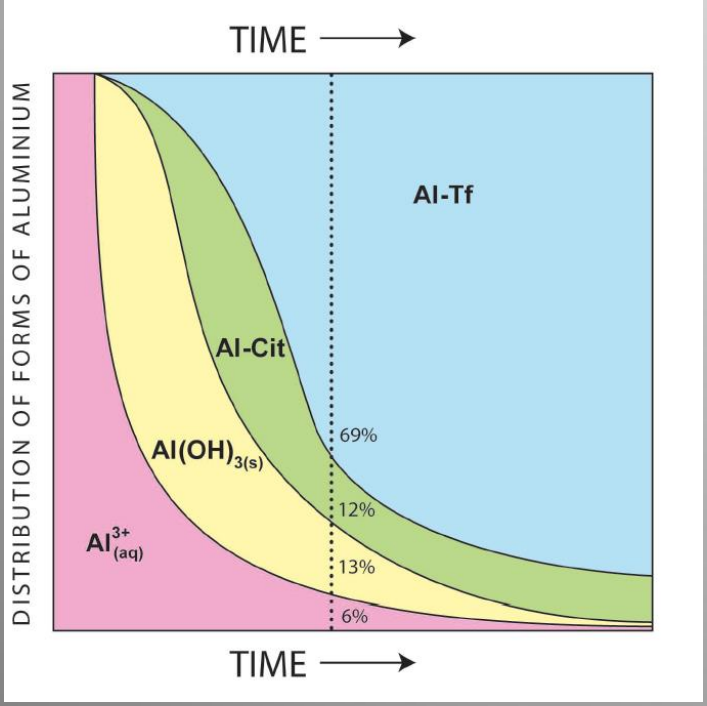
The body burden of aluminium is the sum of aluminium atoms associated with the body at any one moment in time. It includes aluminium on the surface of the skin, aluminium in hair and nails, aluminium associated with external secretions/excretions in the mouth, nose, ear, lung, stomach, small intestine, urinary and reproductive tracts and aluminium in faeces in the large intestine. It also includes aluminium associated with all of the systemic compartments including endo/epithelia, blood, lymph, sweat, tears, humours, tissues, organs and bone.



Exley C (2013) Human exposure to aluminium. Environmental Science:Processes and Impacts 15, 1807-1816.

All forms of Al(III) should be considered as vehicles for the delivery of $Al^{3+}_{(aq)}$ to target sites, usually incorporating oxygen-based functional groups such as carboxylates and phosphates.

Chemical equilibrium suggests the nature of such interactions while non-equilibrium dynamics determine the actual fate in vivo!
For example the fate of Al(III) in serum.



Exley C (2012) Elucidating aluminium's exposome. Current Inorganic Chemistry 2,3-7.

Aluminium-based adjuvants in immunotherapy are contributor's to an individual's aluminium exposome.

Table 1 Typical dosing regimens used in sub-cutaneous allergy immunotherapy

Context	Criteria	Range
First year	Range of number of injections for up dosing to a maintenance dose	4 to 16 injections [7-10]
	Range of number of injections for remaining first year maintenance course	4 to 12 injections [7-10]
Subsequent years	Range of number of injections for subsequent annual maintenance courses	6 to 12 injections [7-10]
	Recommended number of years of treatment	3 to 5 years [11,12]
Whole course	Range of number of injections for 3 years treatment for a single allergen	Up to 54 injections

An individual might receive as much as 50 mg of aluminium adjuvant as a consequence of a 3 year course of immunotherapy.

Exley C (2014) Aluminium adjuvants and adverse events in sub-cutaneous allergy immunotherapy. Allergy, Asthma and Clinical Immunology 10,4.

Adjuvant/Toxicant Implications for Adverse Events

Reported adverse reactions in individuals receiving allergy immunotherapy;

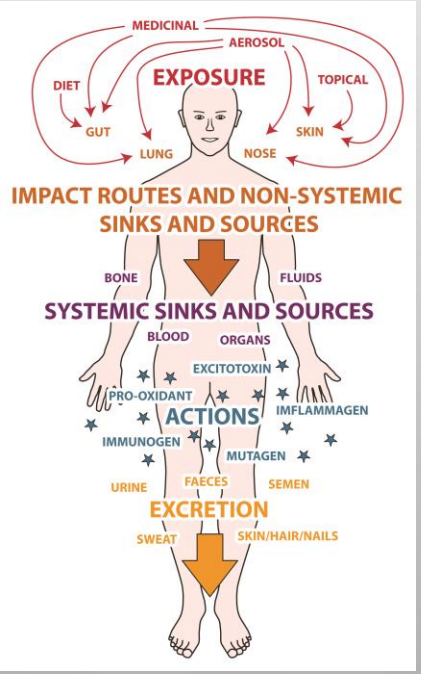
foreign body granulomas, urticaria, sub-cutaneous sarcoidosis, progressive circumscribed sclerosis, sub-cutaneous nodules, cutaneous-sub-cutaneous pseudolymphoma.

The European Medicines Agency (EMA) lists as many as 32 adverse reactions to immunotherapy ranging from discolouration of the skin to encephalopathy.

Exley C (2014) Aluminium adjuvants and adverse events in sub-cutaneous allergy immunotherapy. Allergy, Asthma and Clinical Immunology 10,4.

Mechanisms of Adverse Events?

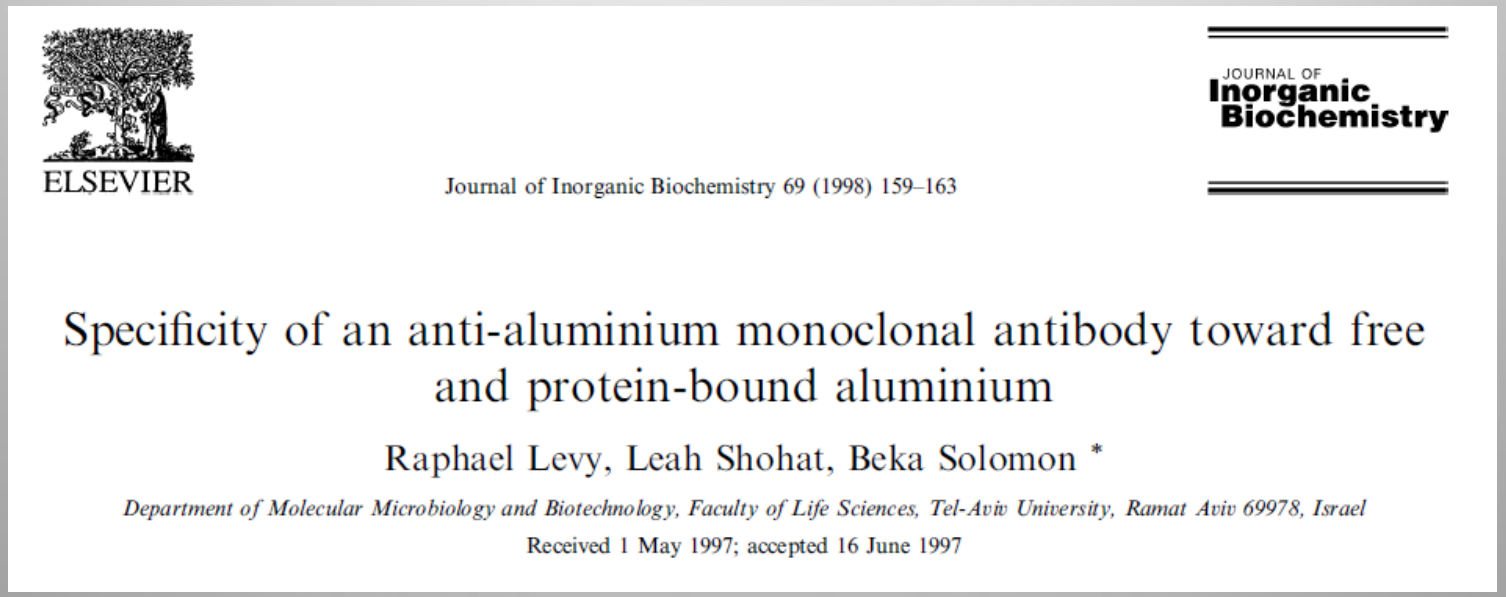
Aluminium body burden?



Do individuals receiving immunotherapy have a higher than ‘usual’ body burden of aluminium?

Mechanisms of Adverse Events?

Aluminium as an antigen?



ELSEVIER

Journal of Inorganic Biochemistry 69 (1998) 159–163

JOURNAL OF Inorganic Biochemistry

Specificity of an anti-aluminium monoclonal antibody toward free and protein-bound aluminium

Raphael Levy, Leah Shohat, Beka Solomon *

Department of Molecular Microbiology and Biotechnology, Faculty of Life Sciences, Tel-Aviv University, Ramat Aviv 69978, Israel

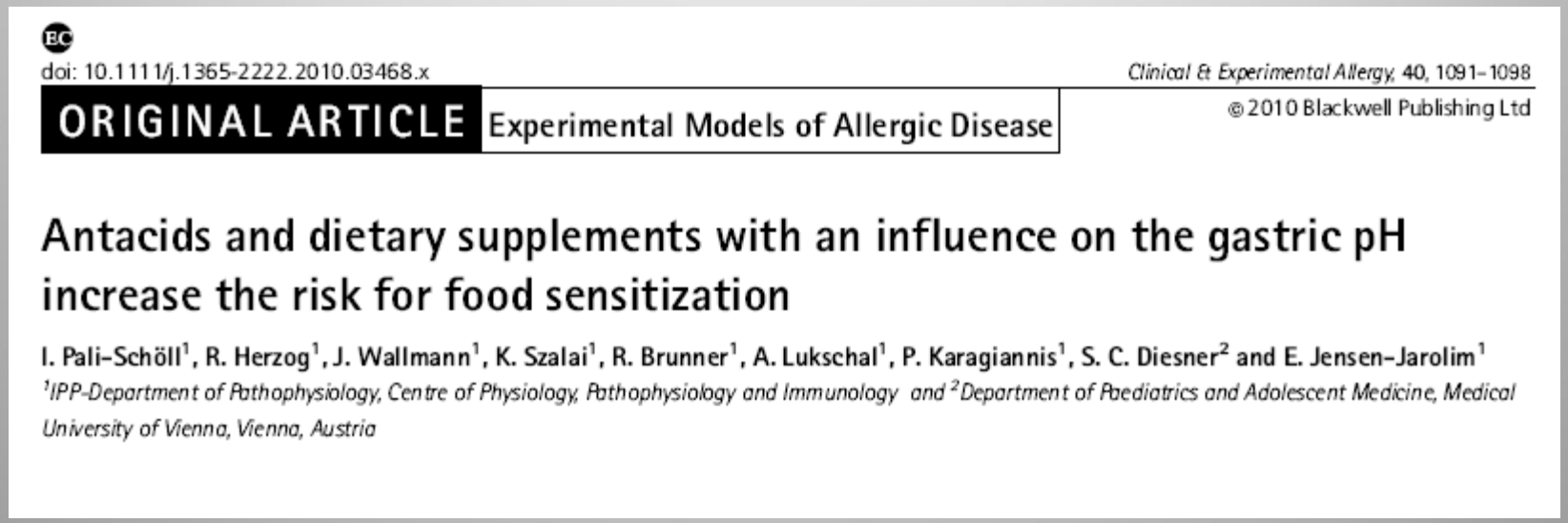
Received 1 May 1997; accepted 16 June 1997

Do individuals receiving immunotherapy demonstrate a ‘memory’ of previous exposures to aluminium?

Exley C, Swarbrick L, Gheradi R & Authier J-F (2009) A role for the body burden of aluminium in vaccine-associated macrophagic myofasciitis and chronic fatigue syndrome. Medical Hypotheses 72, 135-139.

Mechanisms of Adverse Events?

Aluminium as an adjuvant?



doi: 10.1111/j.1365-2222.2010.03468.x

Clinical & Experimental Allergy, 40, 1091–1098

ORIGINAL ARTICLE Experimental Models of Allergic Disease

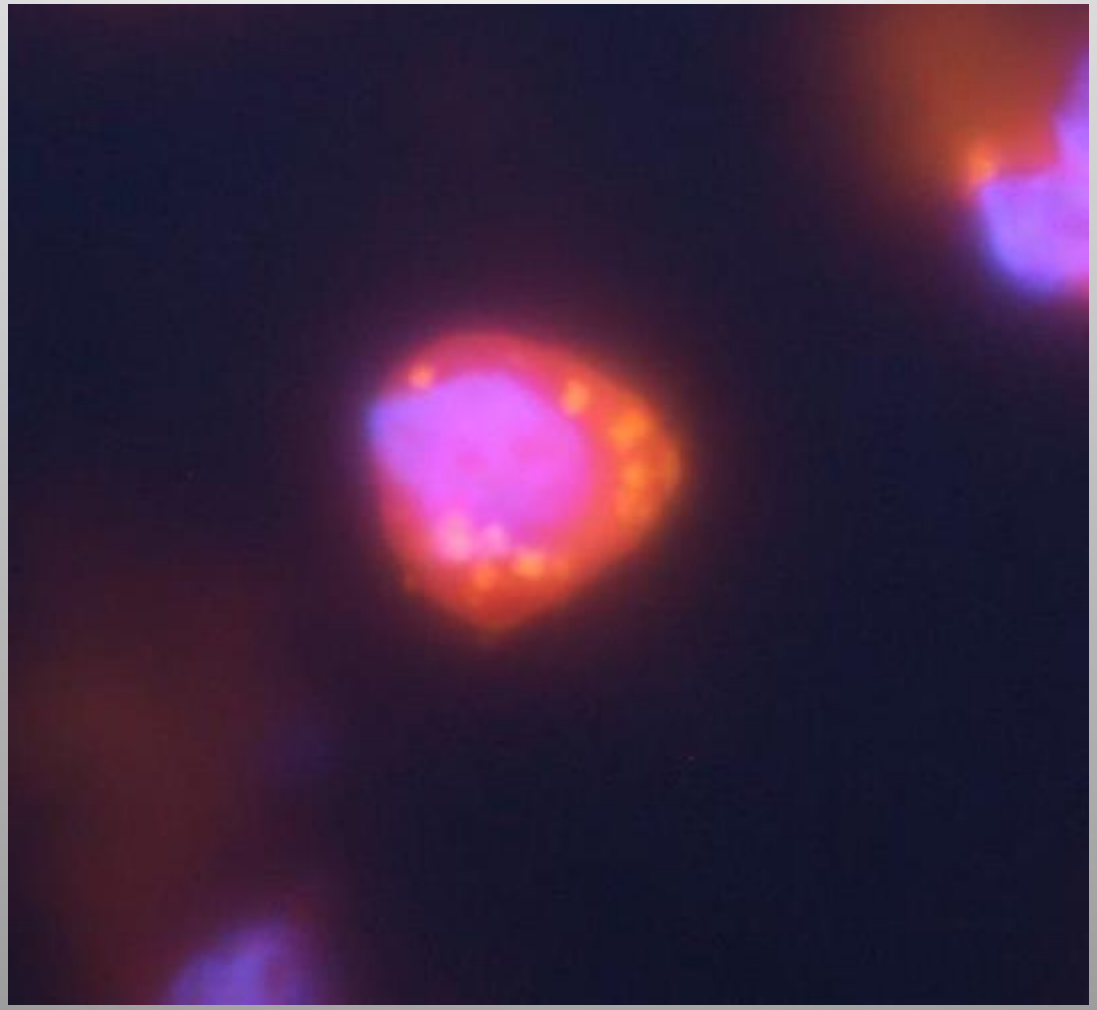
Antacids and dietary supplements with an influence on the gastric pH increase the risk for food sensitization

I. Pali-Schöll[1], R. Herzog[1], J. Wallmann[1], K. Szalai[1], R. Brunner[1], A. Lukschal[1], P. Karagiannis[1], S. C. Diesner[2] and E. Jensen-Jarolim[1]

[1]IPP-Department of Pathophysiology, Centre of Physiology, Pathophysiology and Immunology and [2]Department of Paediatrics and Adolescent Medicine, Medical University of Vienna, Vienna, Austria

Do individuals receiving immunotherapy become sensitised to other environmental/dietary factors (in addition to the allergen)?

Adjuvants in Immunotherapy
A Cause for Concern?



Mold M, Eriksson H, Siesjö P, Darabi A, Shardlow E, Exley C. Unequivocal identification of intracellular aluminium adjuvant in a monocytic THP-1 cell line. Sci Rep 2014; *in press*.

Khan *et al. BMC Medicine* 2013, **11**:99
http://www.biomedcentral.com/1741-7015/11/99

BMC Medicine

RESEARCH ARTICLE Open Access

Slow CCL2-dependent translocation of biopersistent particles from muscle to brain

Zakir Khan[1,2], Christophe Combadière[3,4,5], François-Jérôme Authier[1,2,6], Valérie Itier[1,2,11], François Lux[7,8], Christopher Exley[9], Meriem Mahrouf-Yorgov[1,2,11], Xavier Decrouy[1,2], Philippe Moretto[10], Olivier Tillement[7,8], Romain K Gherardi[1,2,6,12*†] and Josette Cadusseau[1,2,11,12*†]

Conclusion: Nanomaterials can be transported by monocyte-lineage cells to DLNs, blood and spleen, and, similarly to HIV, may use CCL2-dependent mechanisms to penetrate the brain. This occurs at a very low rate in normal conditions explaining good overall tolerance of alum despite its strong neurotoxic potential. However, continuously escalating doses of this poorly biodegradable adjuvant in the population may become insidiously unsafe, especially in the case of overimmunization or immature/altered blood brain barrier or high constitutive CCL-2 production.

Better understanding of the translocation of aluminium adjuvant from the injection site will offer insight both into the mechanism of action of aluminium adjuvants and their potential to exert adverse events in susceptible individuals.

LILLE-FRANCE

Birchall Center, Keele University,
DigestScience Foundation
Lille University
Present the

11th Keele Meeting On Aluminium

The Natural History of Aluminium
Past, Present and Future

Saturday, February 28 to Wednesday, March 4, 2015
Hôtel couvent des minimes, Lille

Keele University

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2014

Thank you!