Human Exposure to Aluminium
Aluminium Age and/or Aluminium Tyranny?

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

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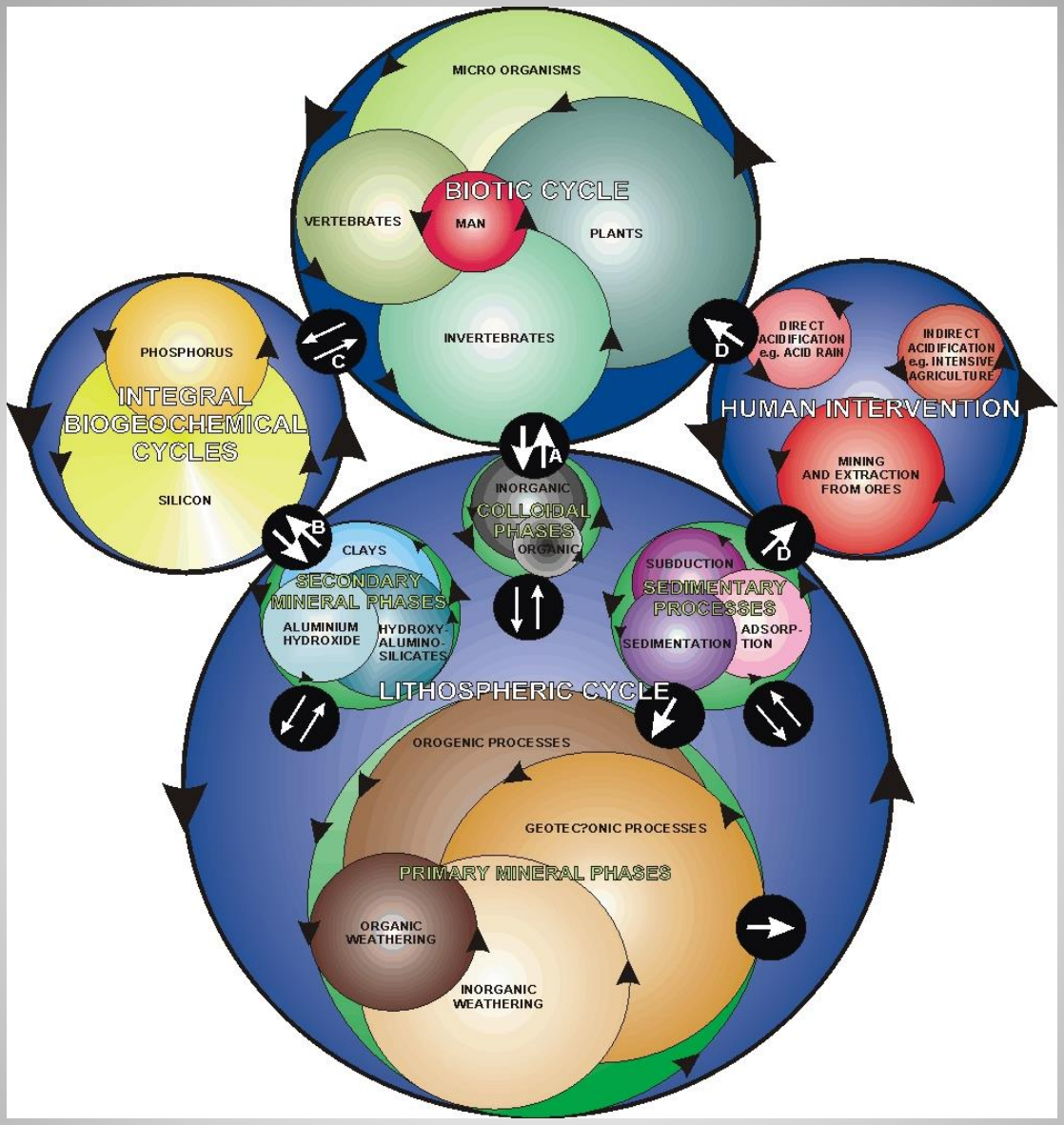
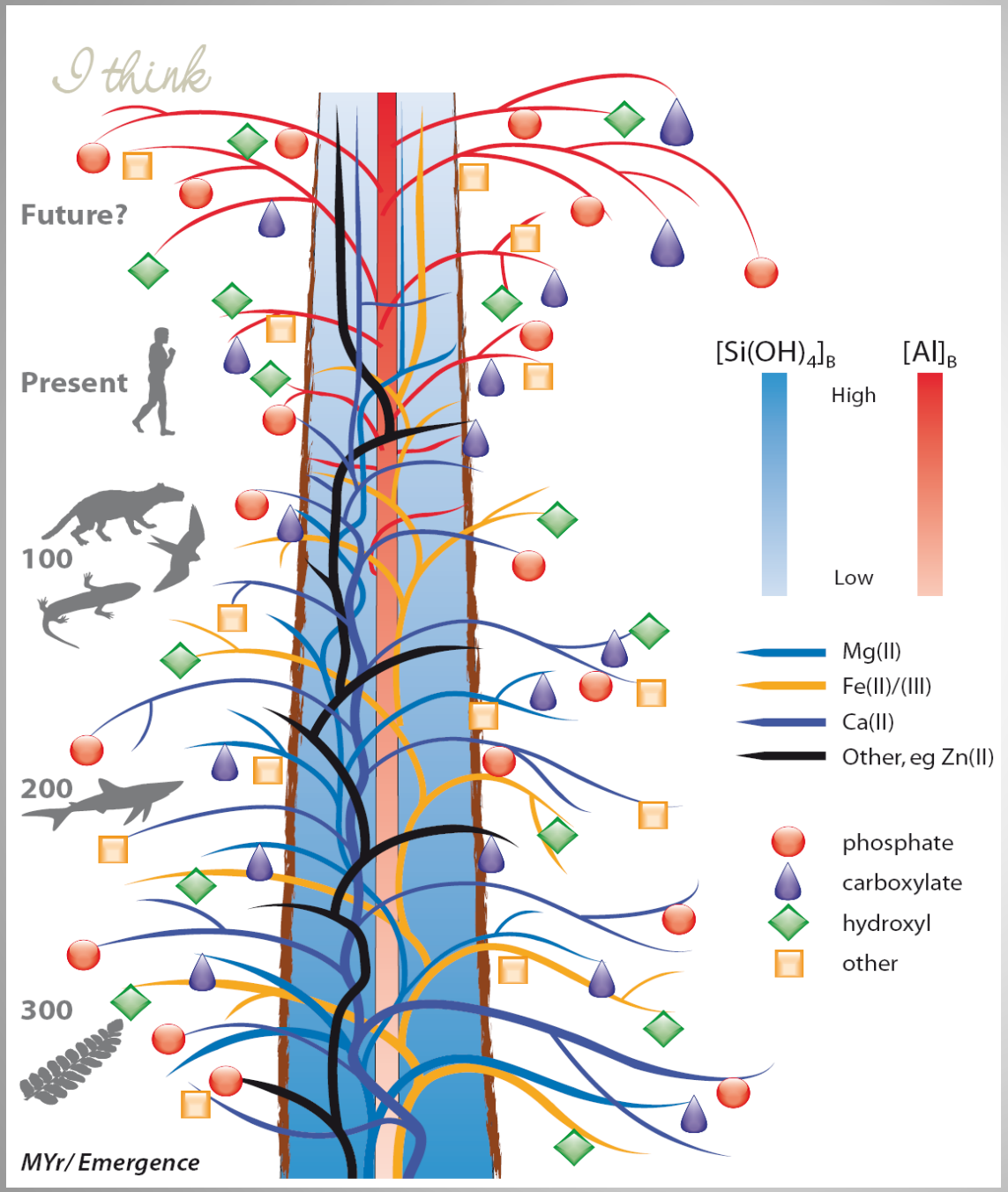


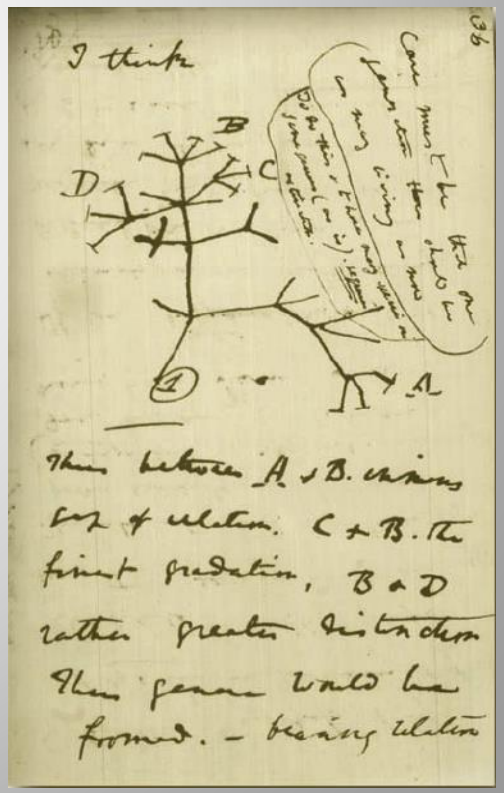
THE BIOGEOCHEMICAL CYCLE OF ALUMINIUM

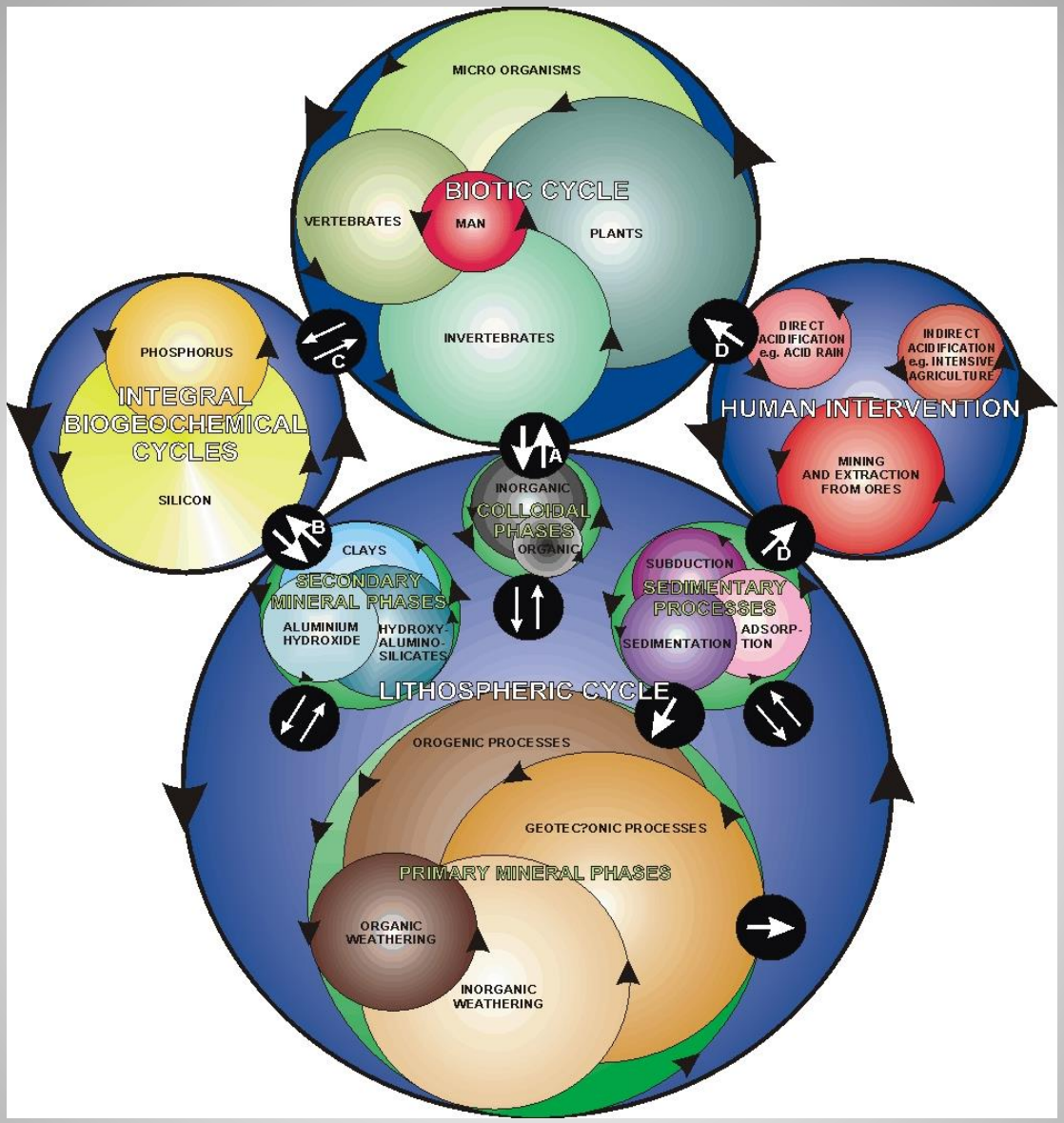
Exley C (2003) A biogeochemical cycle for aluminium ? J. Inorg. Biochem. 97, 1-7.

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.



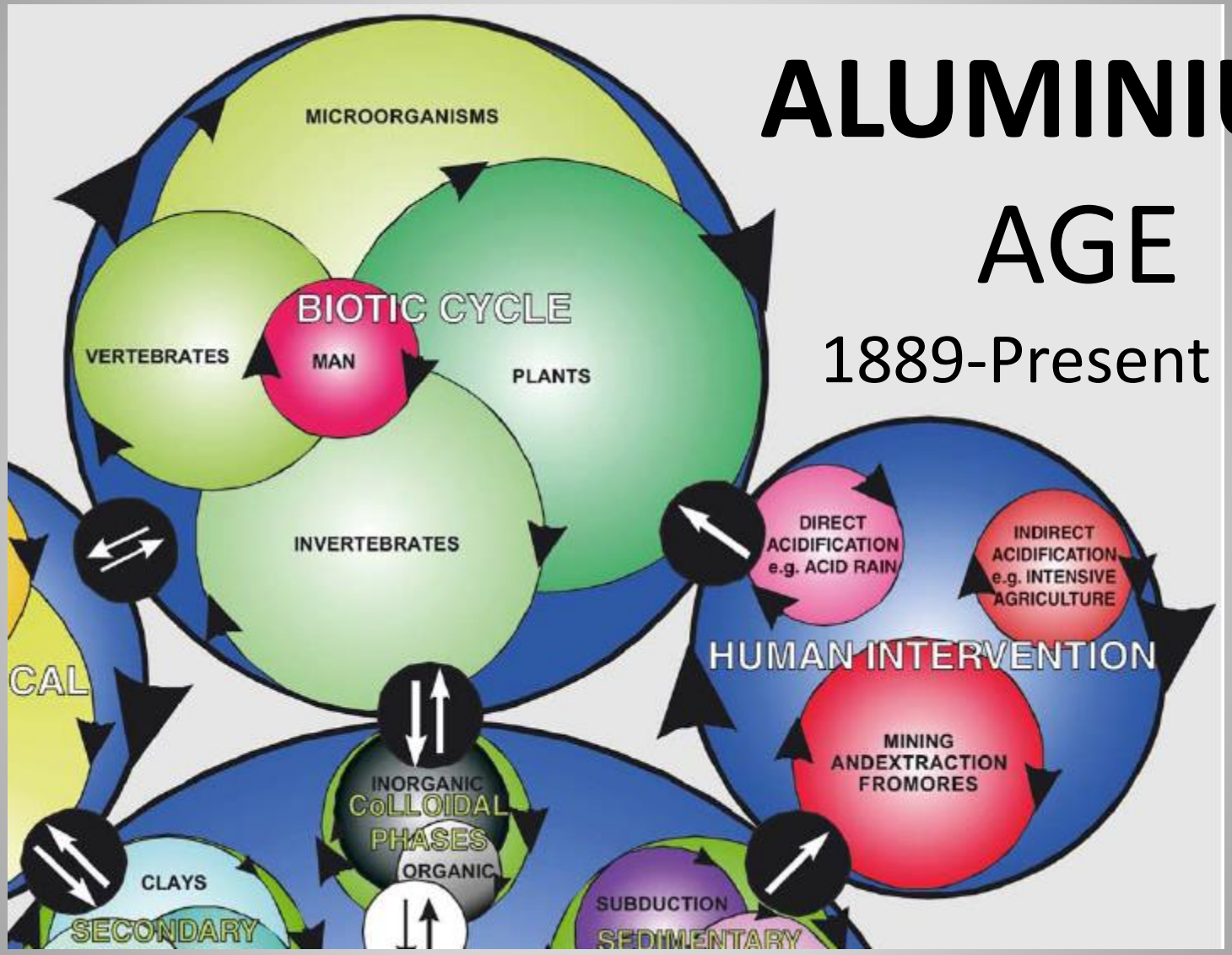


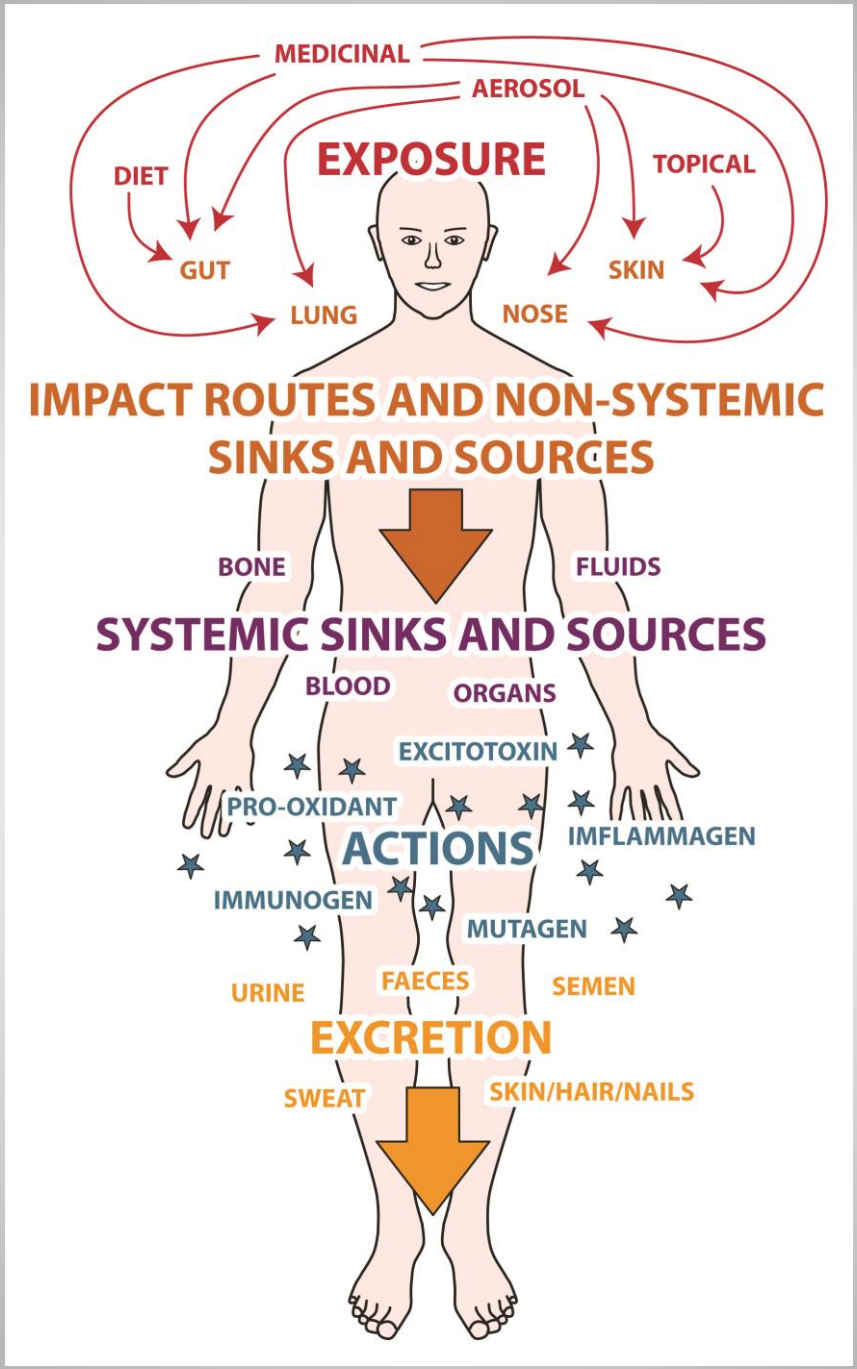
THE BIOGEOCHEMICAL CYCLE OF ALUMINIUM

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

THE **ALUMINIUM** AGE

1889-Present Day



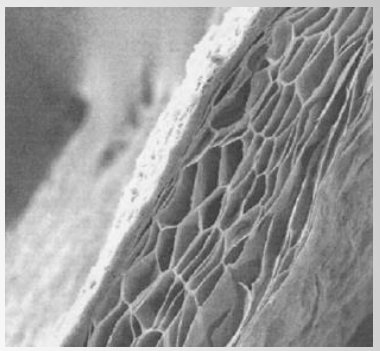


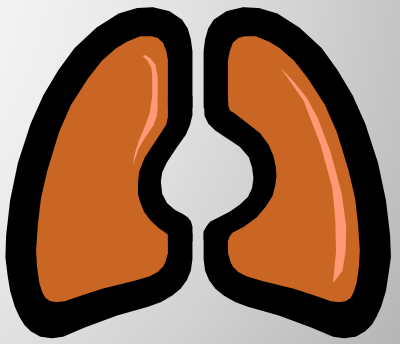
Exley C (2013) Human exposure to aluminium. Environmental Science:Processes and Impacts 15, 1807-1816.

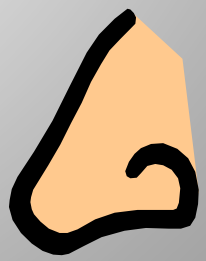
The Body Burden of **Aluminium**: What is it?


EXPOSURE
↔
BURDEN
↔
EXCRETION

EXPOSURE

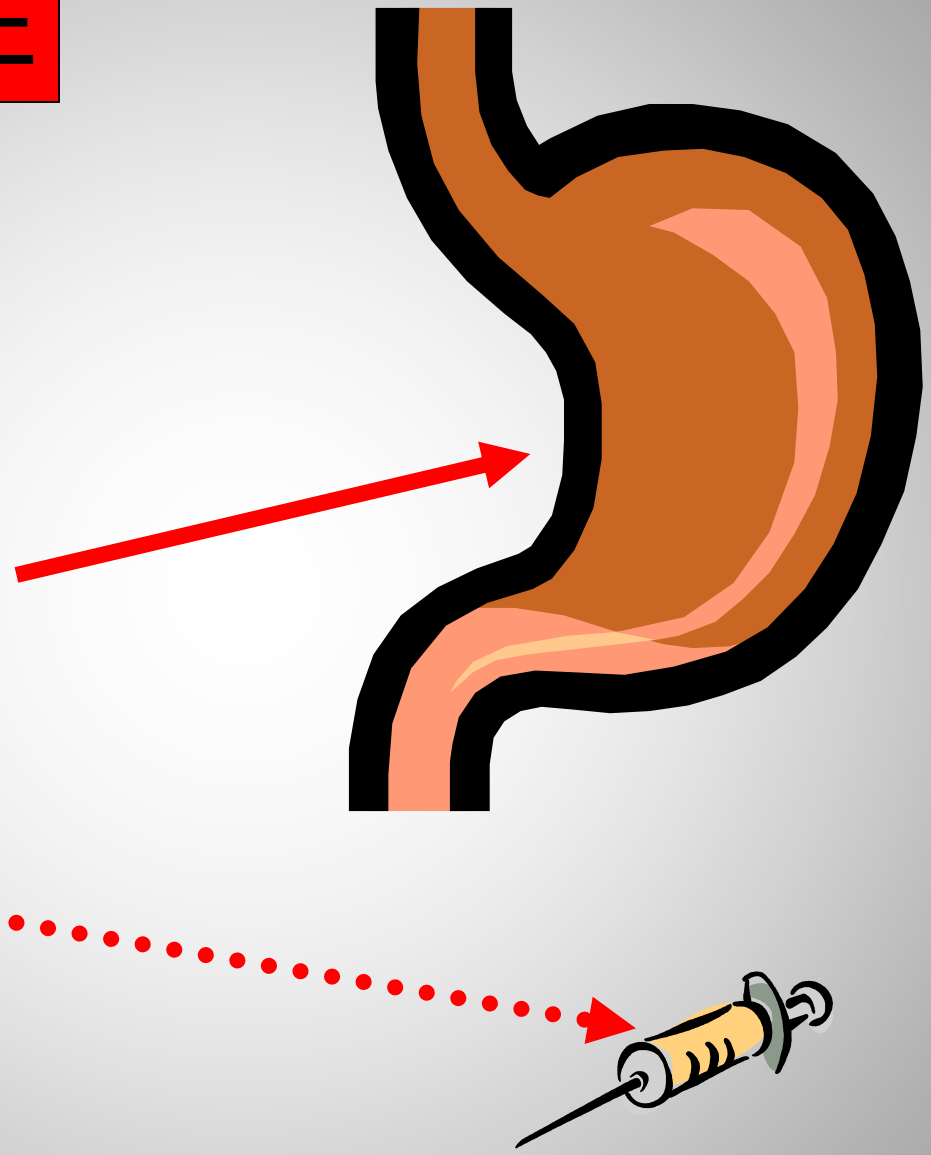






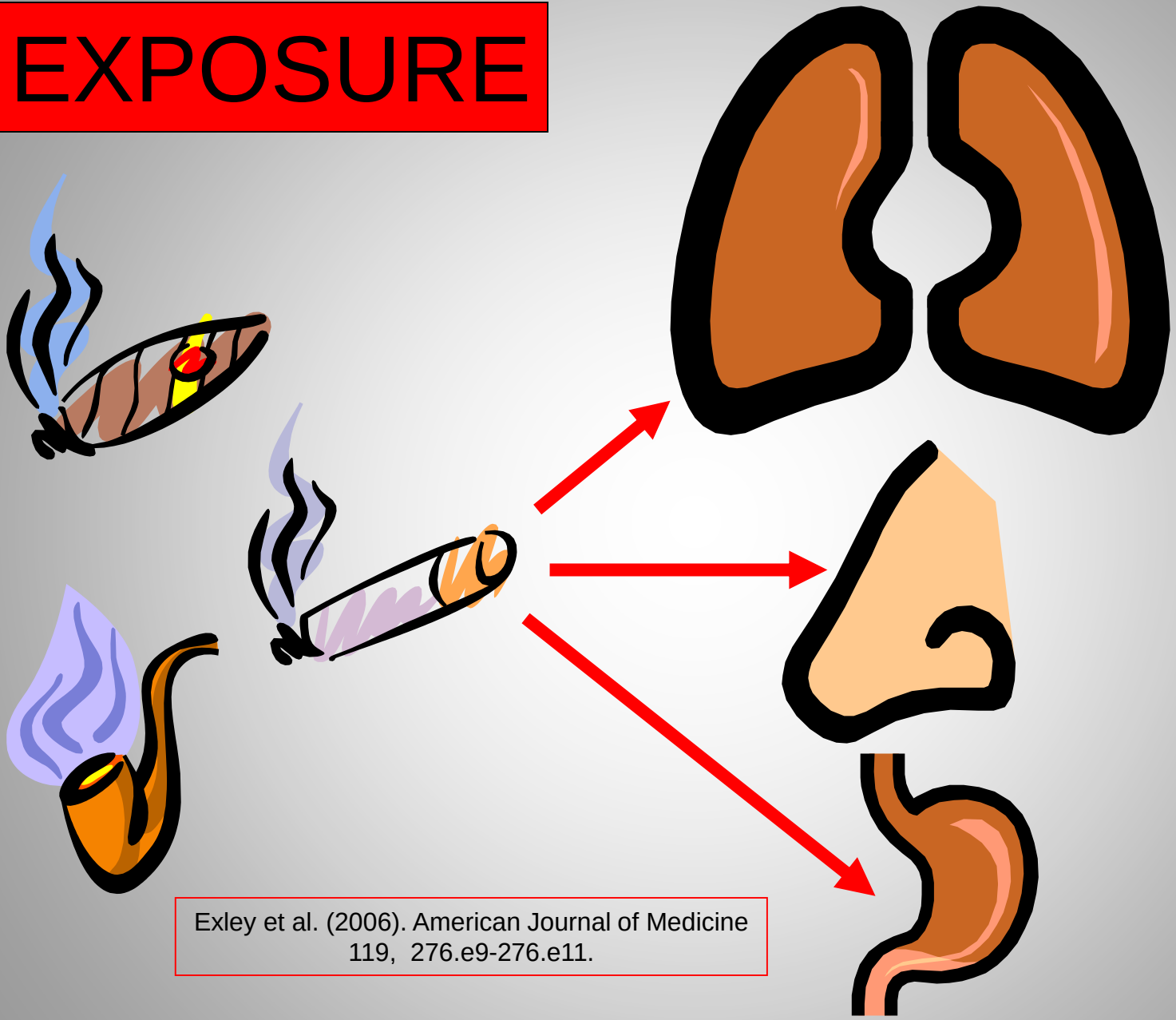
Yokel et al. (2001). Toxicology 16,193-101.

EXPOSURE



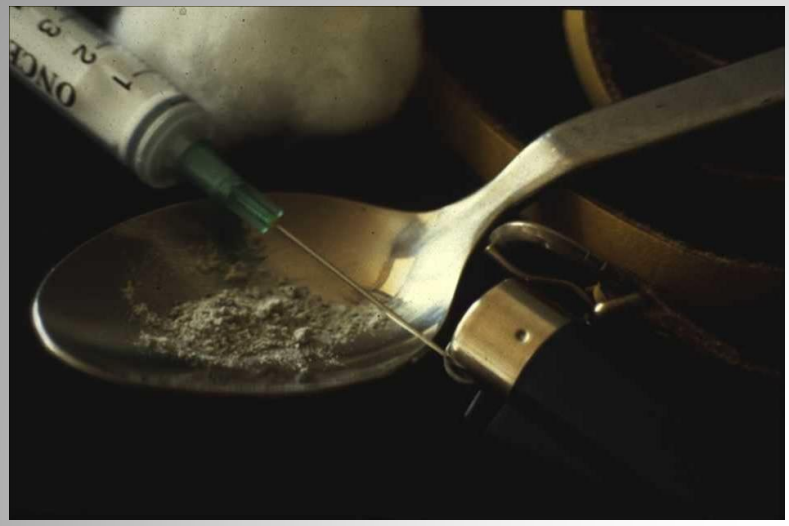
Saiyed & Yokel (2005). Food Additives and Contaminants 22, 234-244.

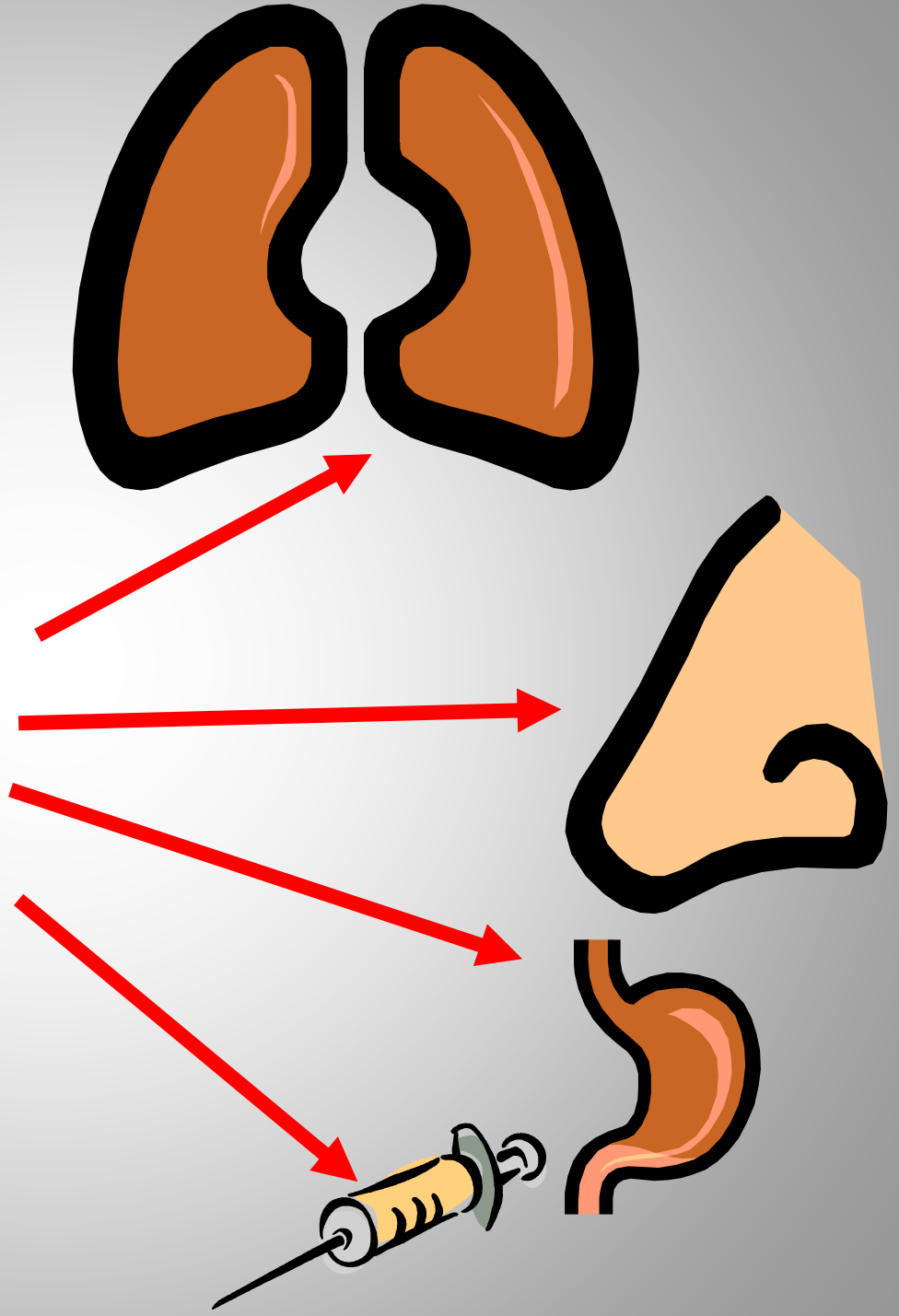
EXPOSURE



Exley et al. (2006). American Journal of Medicine 119, 276.e9-276.e11.

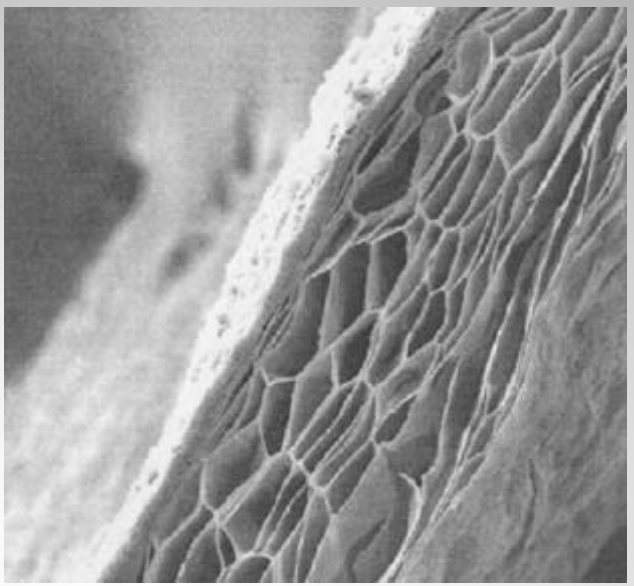
EXPOSURE

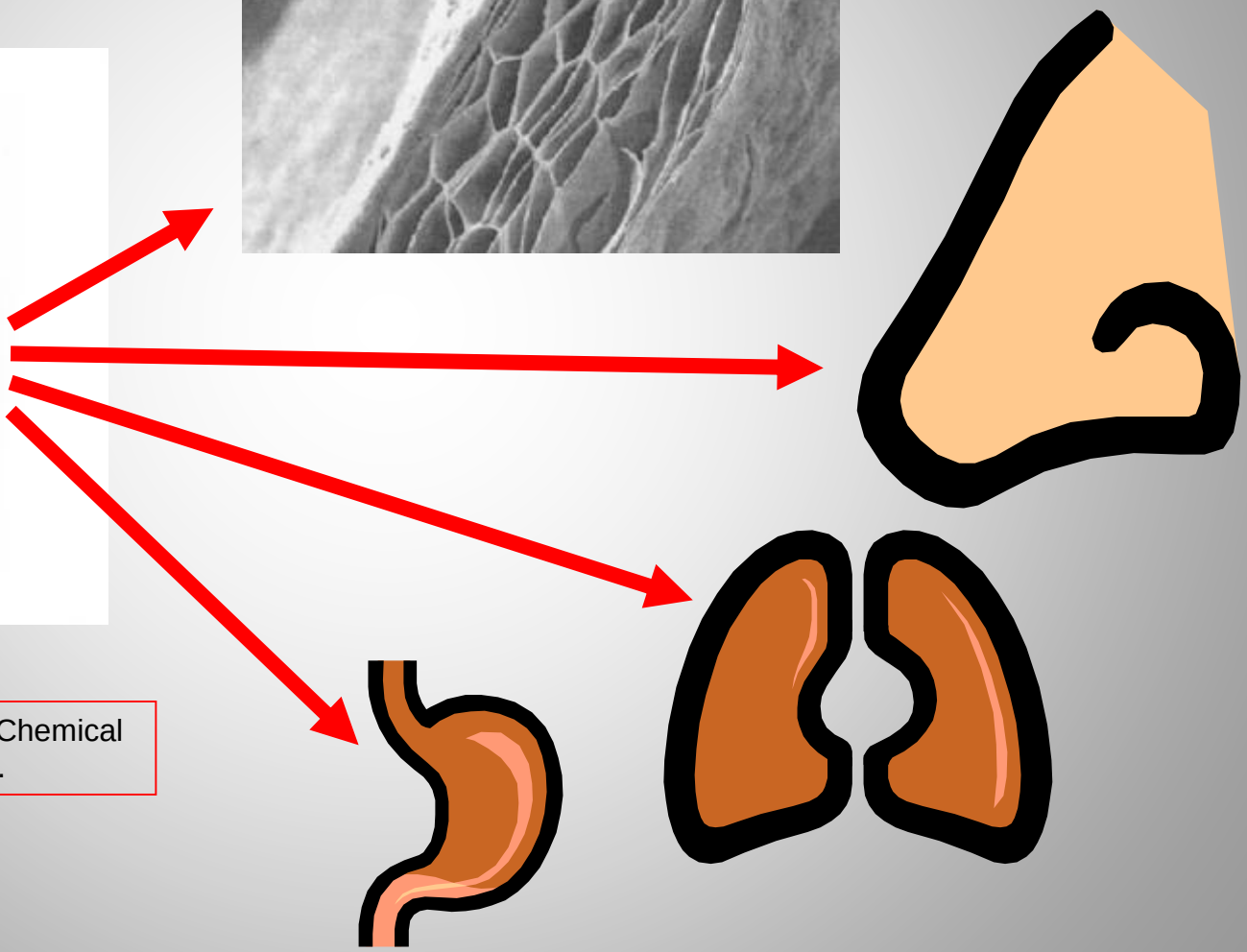




Exley et al. (2007) Addiction Biology 12, 197-199.

EXPOSURE





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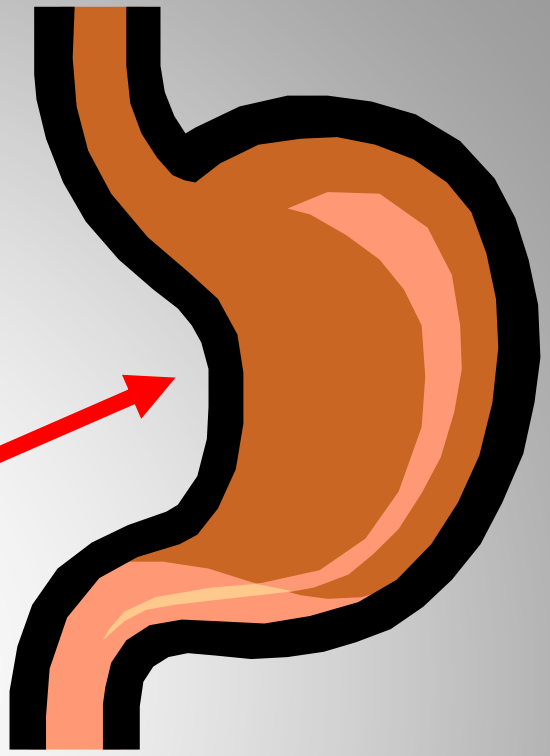
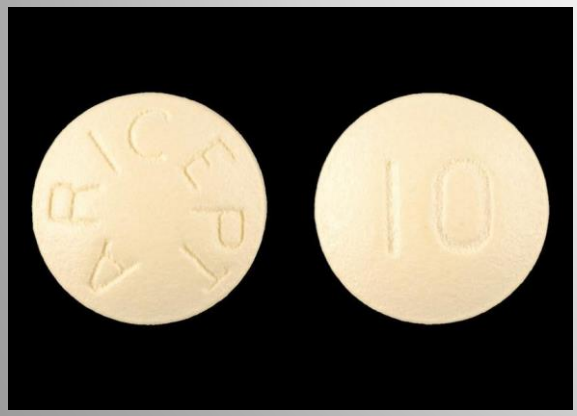
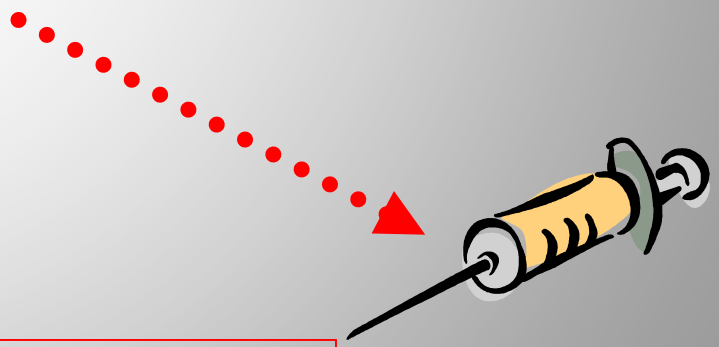
EXPOSURE

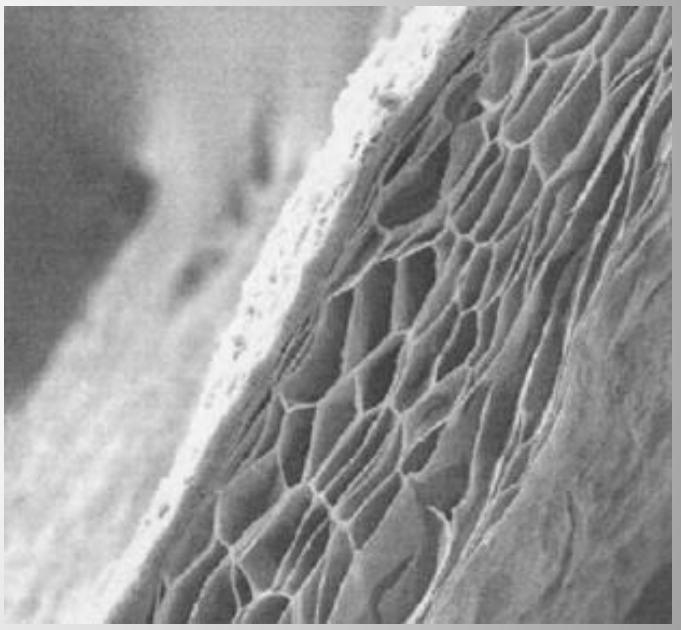






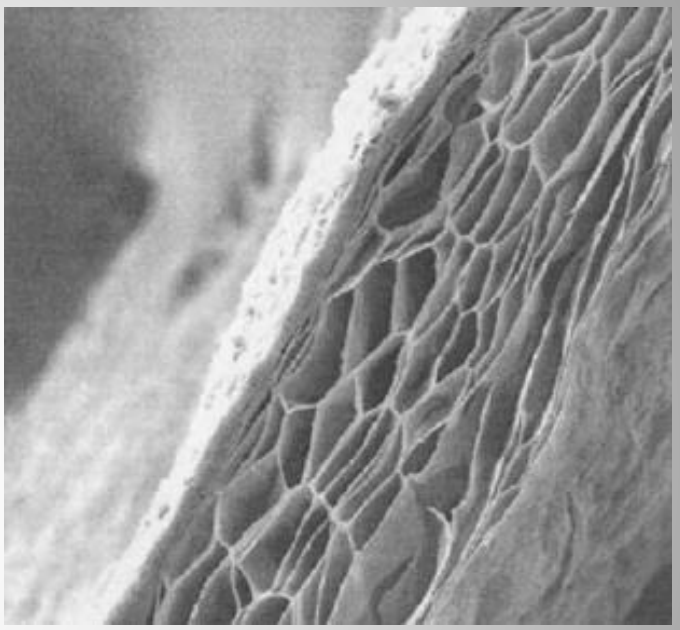
Reinke et al. (2003) Drug Safety 26, 1011-1025.

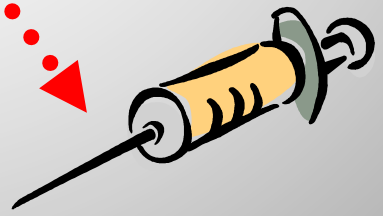
EXPOSURE



Nicholson & Exley (2007) Free Rad Biol Med 43, 1216-1217.

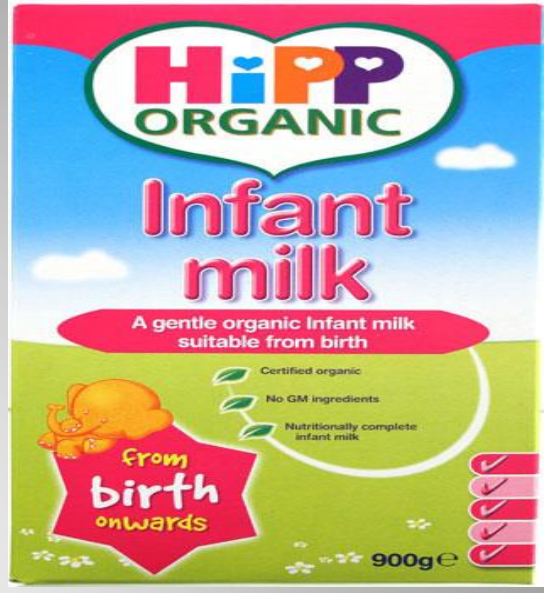
EXPOSURE





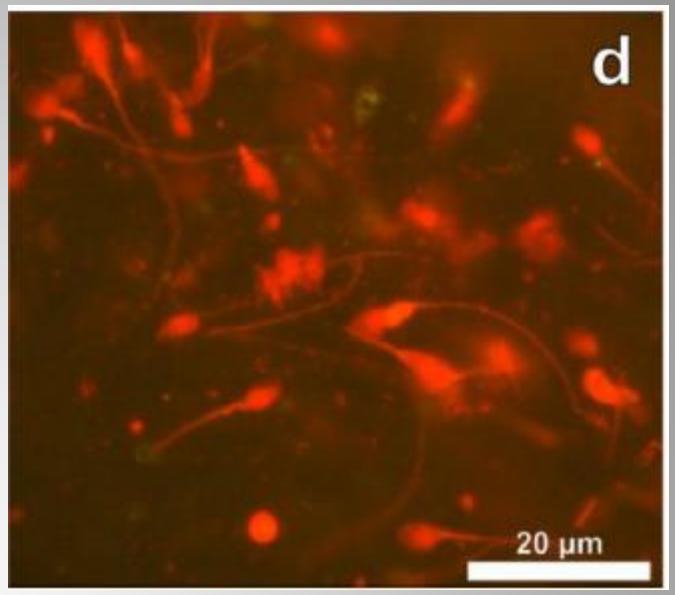
Flarend et al. (1997) Vaccine 15,1314-1318.

EXPOSURE



Burrell & Exley (2010) BMC Pediatrics 10, 63.
Chuchu et al. (2013) BMC Pediatrics 13, 162.

Human exposure to aluminium begins at conception!



Klein JP, Mold M, Mery L, Cottier M and Exley C (2014) Reproductive Toxicology 50, 43-48.

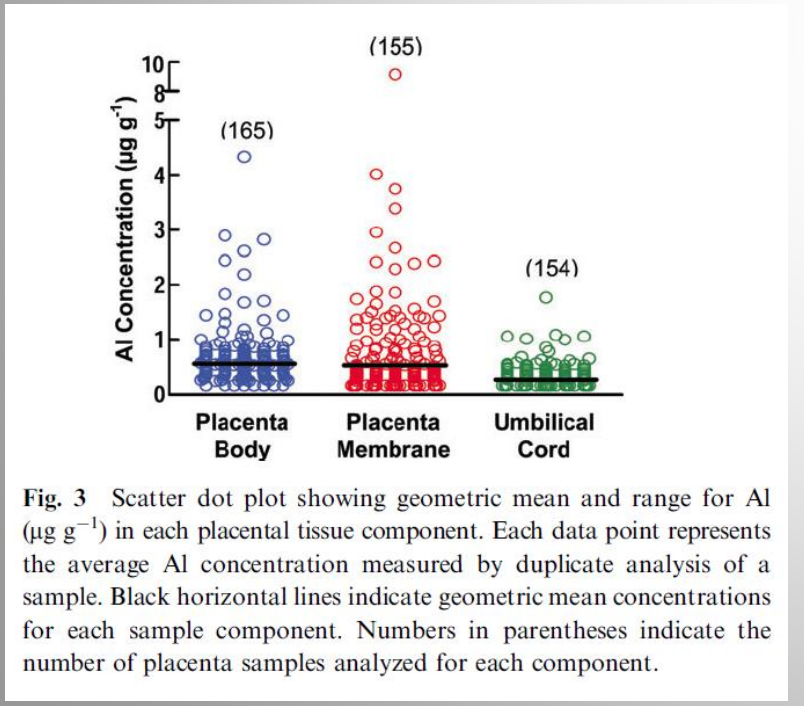
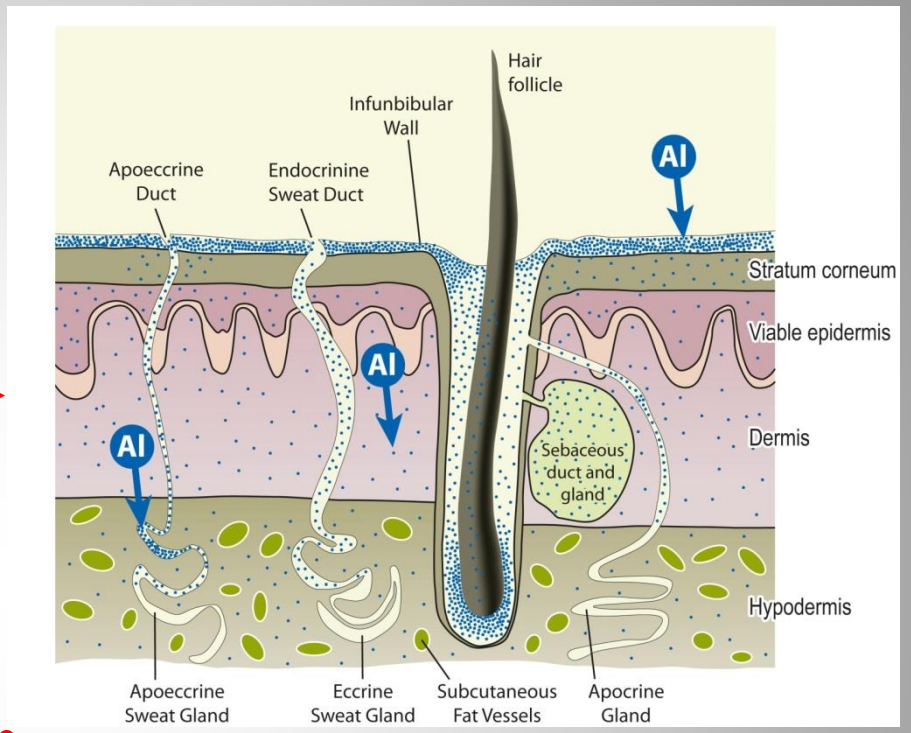
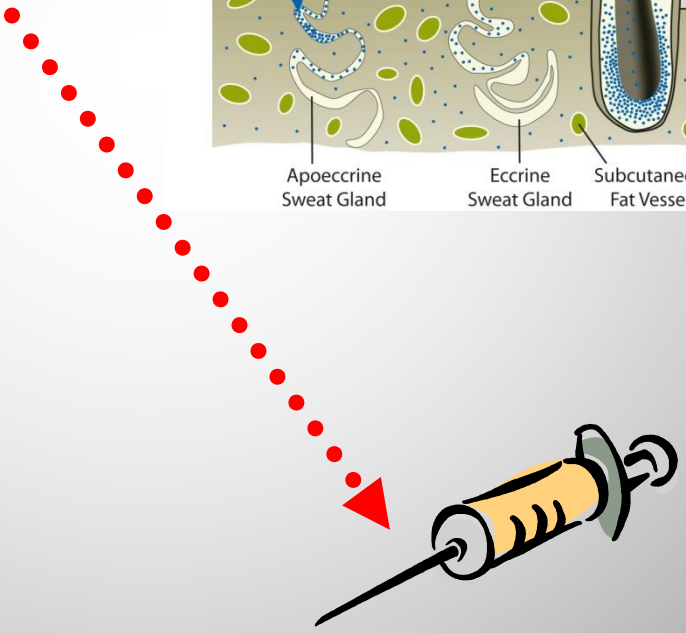


Fig. 3 Scatter dot plot showing geometric mean and range for Al (µg g^{-1}) in each placental tissue component. Each data point represents the average Al concentration measured by duplicate analysis of a sample. Black horizontal lines indicate geometric mean concentrations for each sample component. Numbers in parentheses indicate the number of placenta samples analyzed for each component.

Kruger PC, Schell LM, Stark AD and Parsons PJ (2010) Metallomics 2, 621-627.

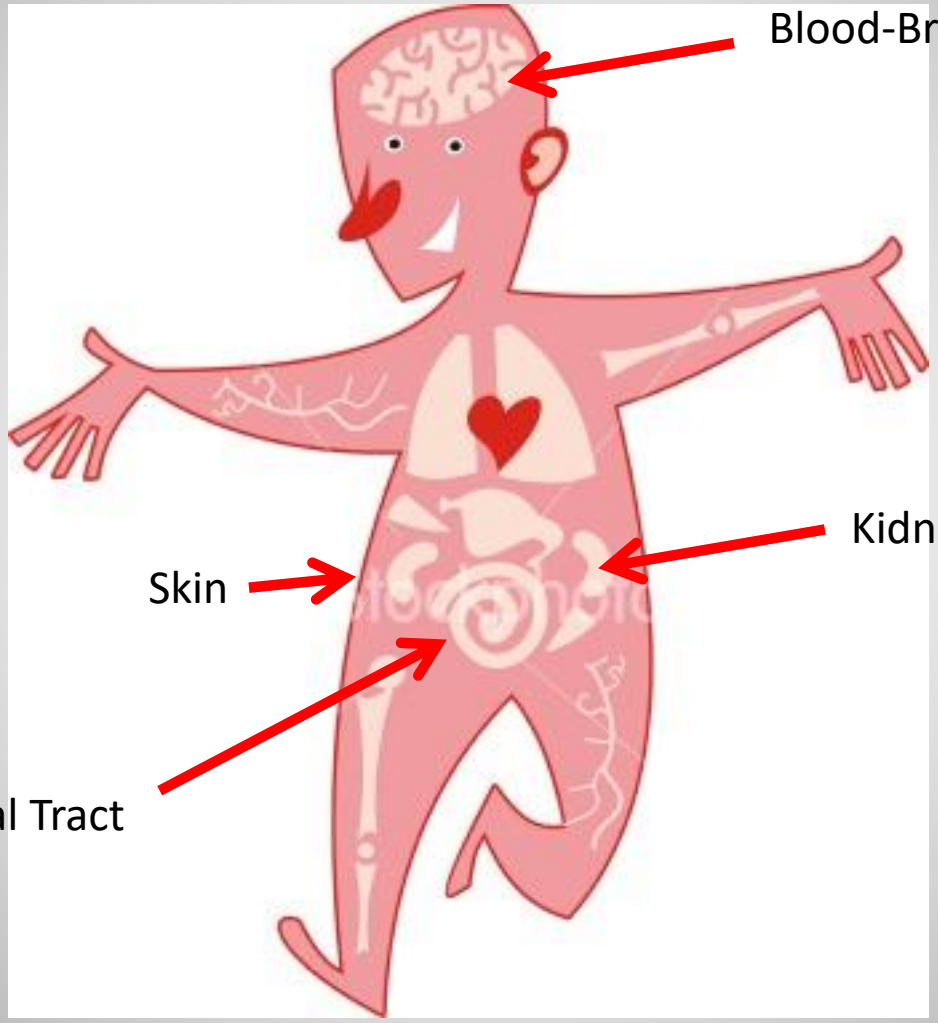
The Burden of Infant Vaccination





Tomljenovic L, Shaw CA (2011) Journal of Inorganic Biochemistry 105, 1489-1499.
Tomljenovic L, Shaw CA (2012) Lupus 21, 223-230.

The Infant (and Especially the Neonate) is a Special Case



EXPOSURE

Dental Cements?

Demirkaya et al. (2016) Eur J Oral Sci 124, 75-81.*
Nicholson JW & Czamecka B (2009) J Biomat Appl 24, 293-308

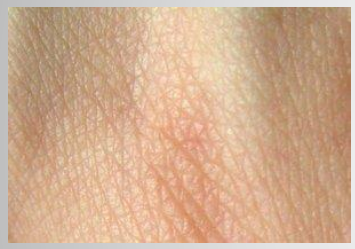
*..Al might have been released into the circulation from the three dental cements tested, especially MTA Angelus and MTA Fillapex.

Toothpastes?

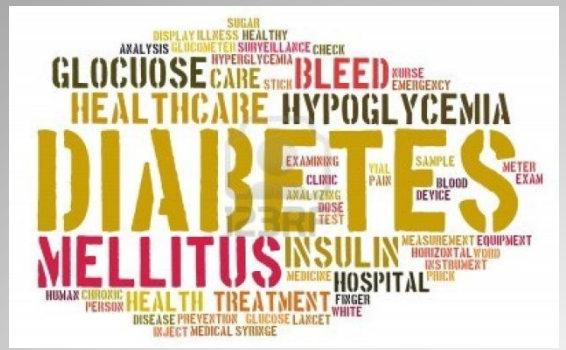
Heidmann J & Polusen S (1997) Caries Res 31, 85-90.
Rajwanshi et al. (1997) Sci Tot Environ 193, 243-249.

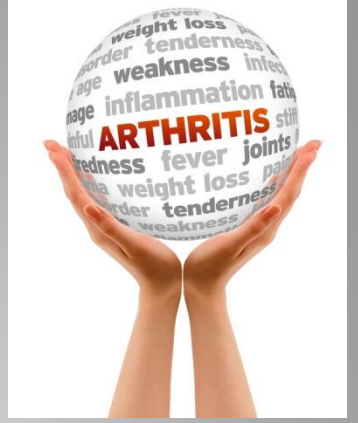
Living in ‘The Aluminium Age’ ensures our body burden of Al

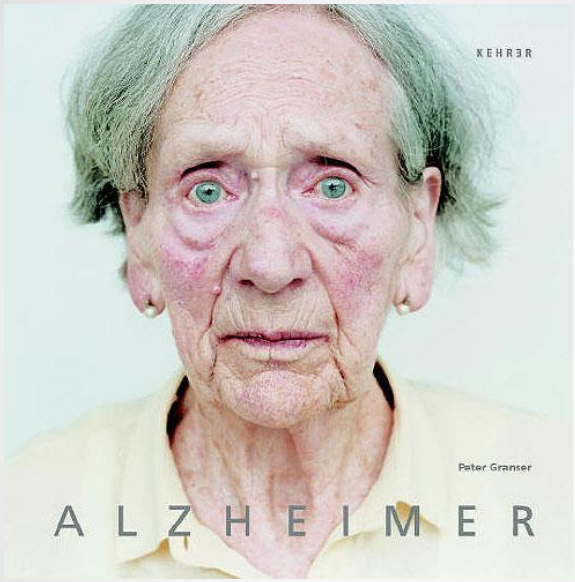
What About Excretion of Aluminium from the Body?

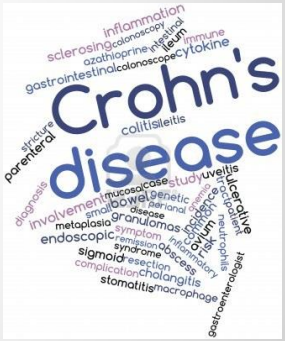


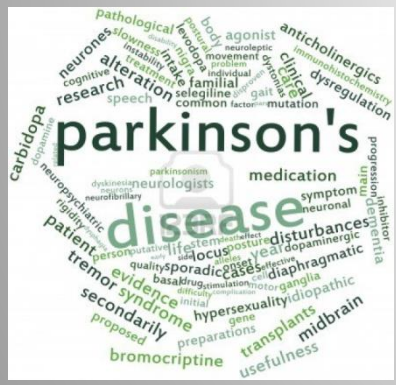
Minshall C et al. (2014) Journal of Trace Elements in Medicine and Biology 28, 87-88





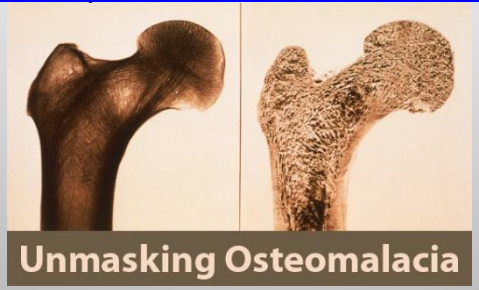




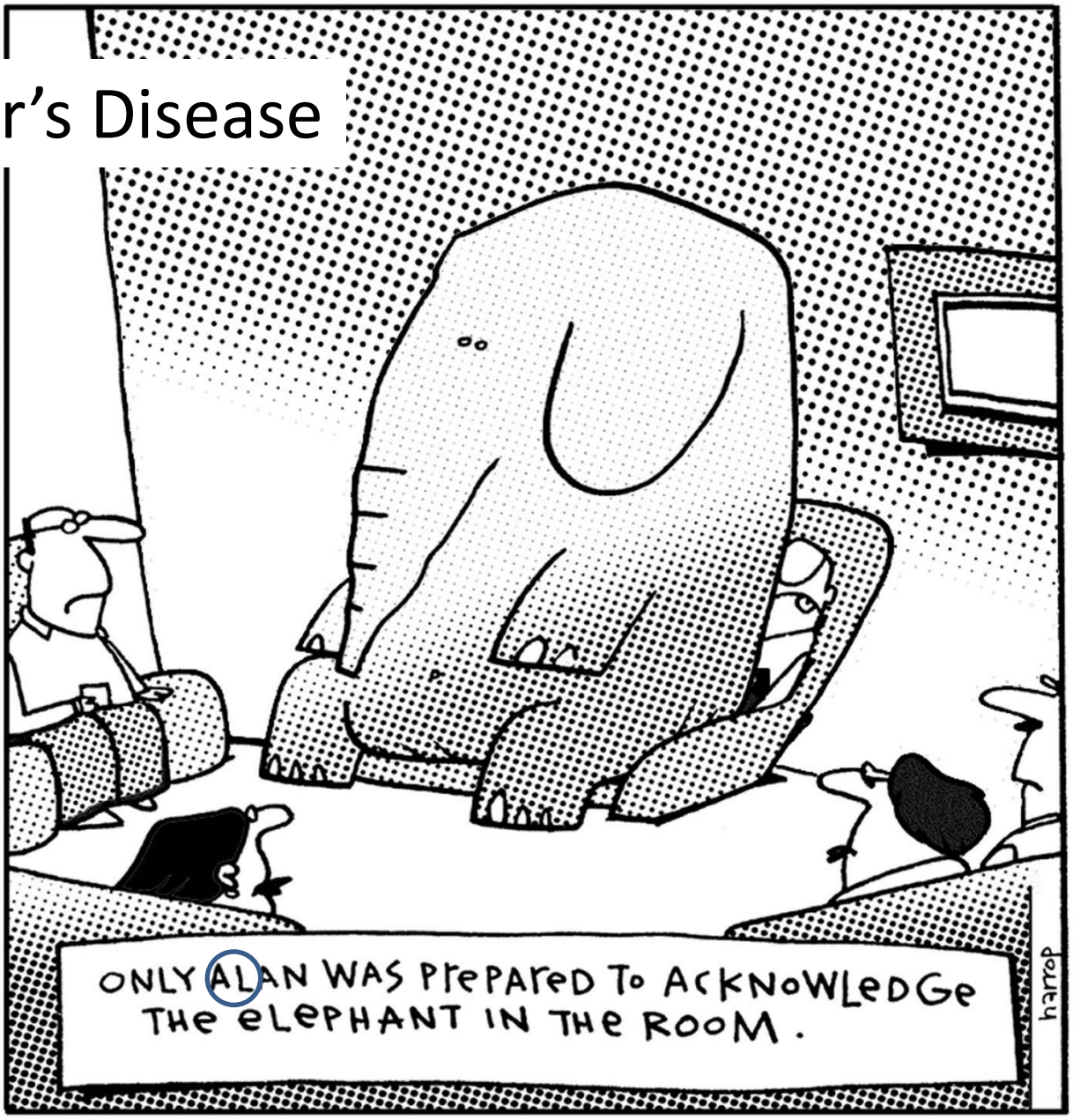


THE **ALUMINIUM** AGE?

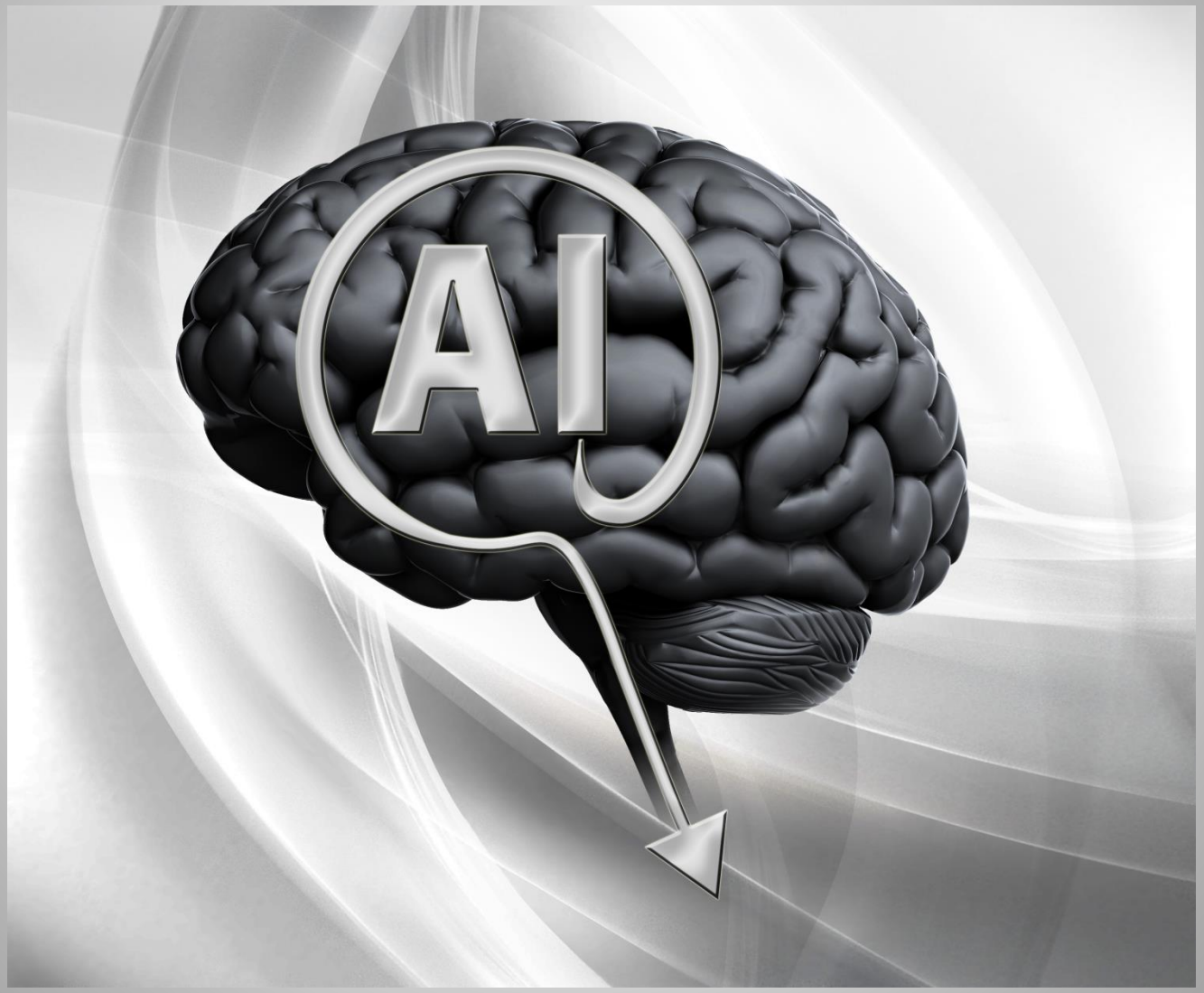
http://www.youtube.com/watch?v=FrYxIVb3qPs



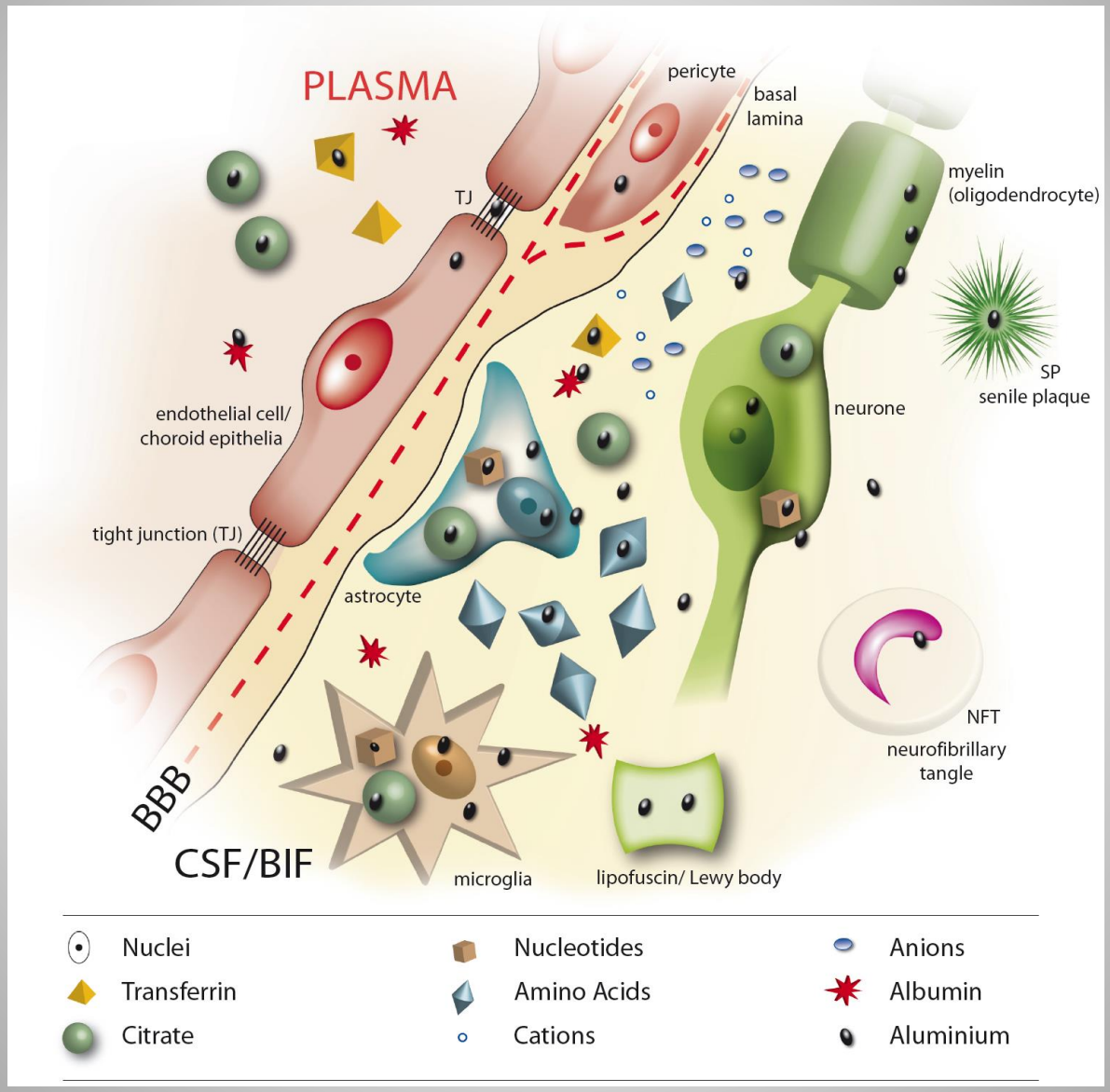
Alzheimer's Disease



Aluminium and The Brain



Aluminium in the Brain



Exley C and House E (2011) Aluminium in the human brain. Monatshefte für Chemie - Chemical Monthly 142, 357-363.

Metallomics

Dynamic Article Links

Cite this: *Metallomics*, 2012, **4**, 56–65

www.rsc.org/metallomics

PAPER

Aluminium, iron and copper in human brain tissues donated to the medical research council's cognitive function and ageing study

Emily House,[a] Margaret Esiri,[b] Gill Forster,[c] Paul G Ince[c] and Christopher Exley*[a]

Sixty Human Brains

>700 tissue digests (250 mg wet weight)

174 Method Blanks; Al = 54 ng Al/vessel (Mean + 1.654SD)

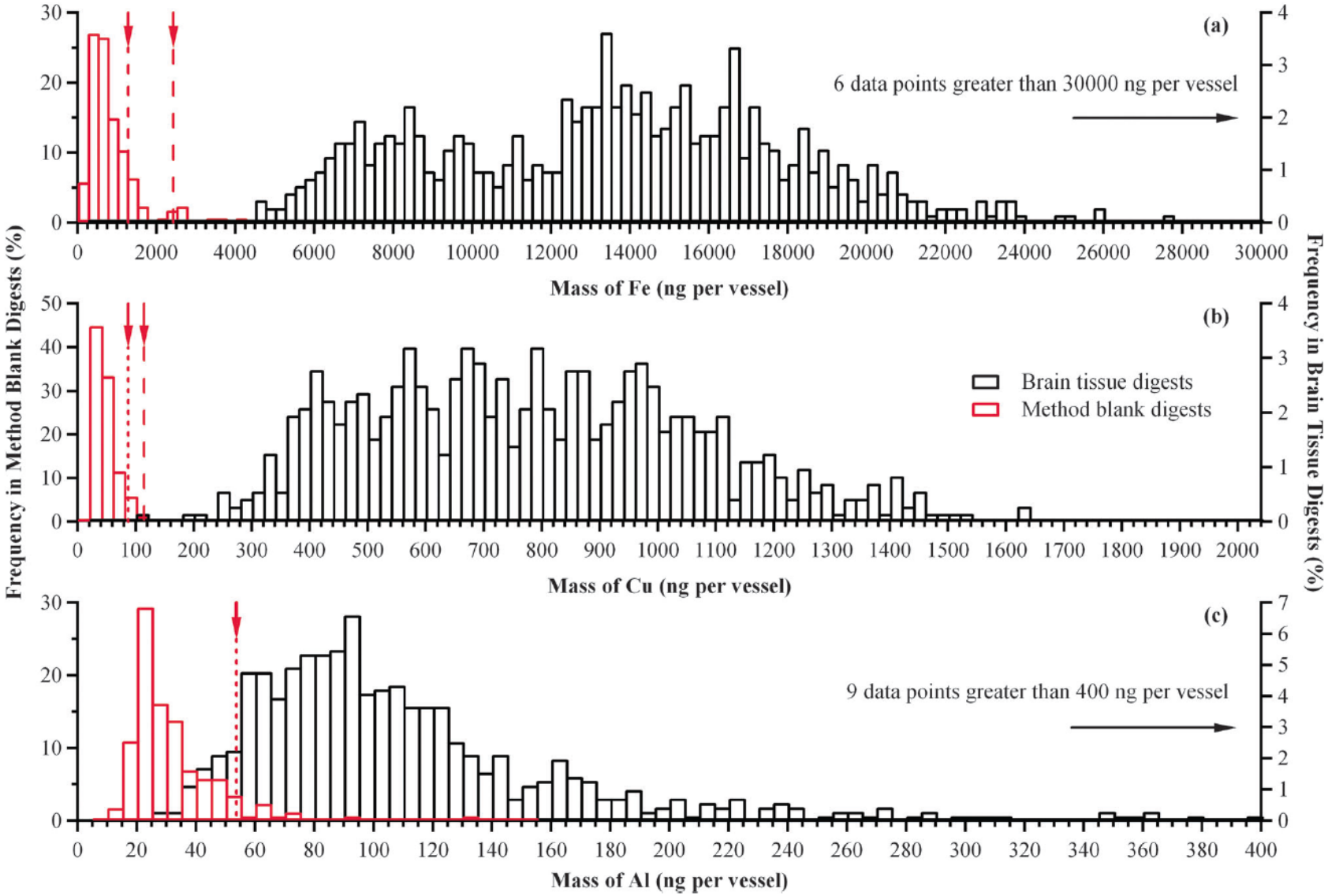


Fig. 2 Mass of (a) Fe, (b) Cu and (c) Al in vessels containing *ca* 5 mL method blank digests and brain tissue digests uncorrected for contamination. Arrows and dashed lines show the contaminant level which was subtracted from tissue digest values.

Aluminium Content of Human Brain

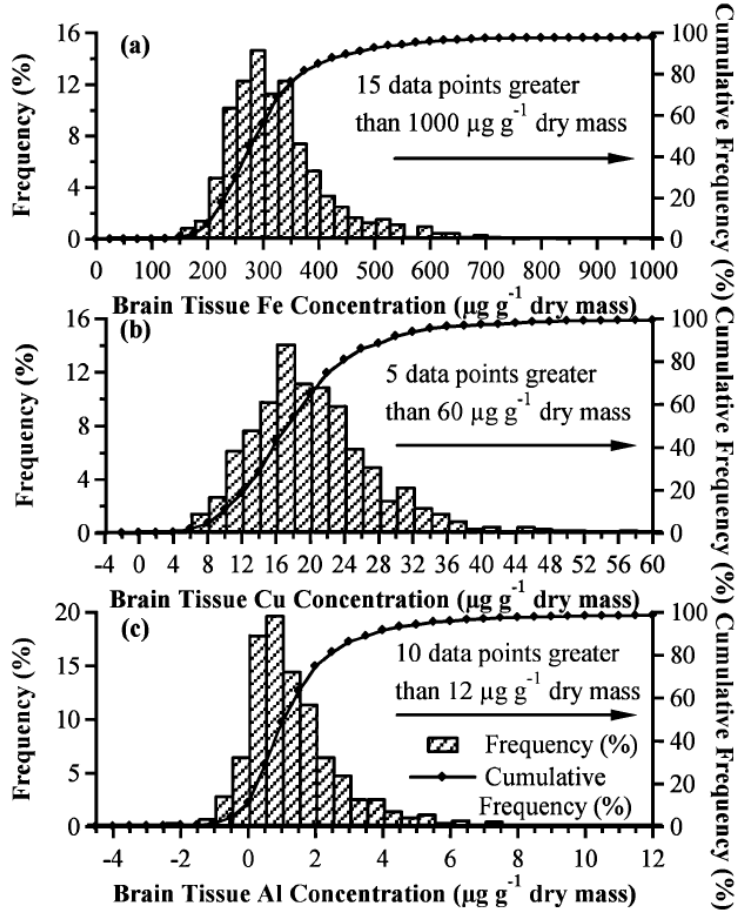


Fig. 3 Percentage frequency (bars) and cumulative frequency (line and marker) distributions of (a) Fe, (b) Cu and (c) Al concentrations in (n = 719, 720 and 713 respectively) brain tissues after subtraction of contamination.

The median Al content of tissues from all **60 brains** (n=713) is 1 µg/g dry wt.

In 52 out of 60 individuals at least one tissue sample exceeded 2 µg Al/g dry wt.

In 41 out of 60 individuals at least one tissue sample exceeded 3.5 µg Al/g dry wt.

Approximately 70% of individuals aged 70 – 103 years had at least one tissue Al content which should be considered as pathological.

House E, Esiri M, Forster G, Ince PG and Exley C (2012) Aluminium, iron and copper in human brain tissues donated to the medical research council's cognitive function and ageing study. Metallomics 4, 56-65.

Accidental Exposure to Aluminium

Camelford, Cornwall, United Kingdom, 1988

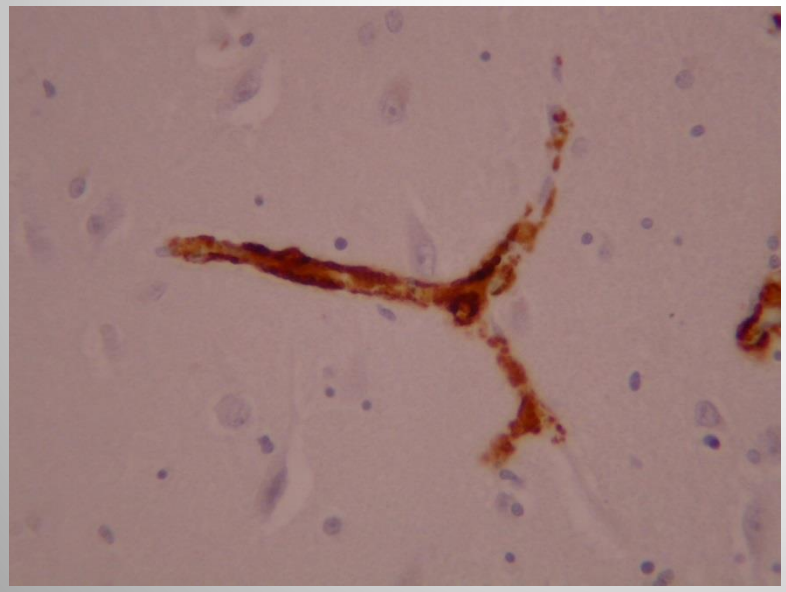
SHORT REPORT

Severe cerebral congophilic angiopathy coincident with increased brain aluminium in a resident of Camelford, Cornwall, UK

C Exley, M M Esiri

See Editorial Commentary, p 811

J Neurol Neurosurg Psychiatry 2006;**77**:877–879. doi: 10.1136/jnnp.2005.086553



Frontal Cortex, n=5.

1. 23.00* μg/g dry wt.
2. 3.24
3. 11.01
4. 4.33
5. 5.71

*Noted during measurement as a heavily vascularised piece of tissue.

Occupational Exposure to Aluminium

Exley and Vickers *Journal of Medical Case Reports* 2014, **8**:41
http://www.jmedicalcasereports.com/content/8/1/41

CASE REPORT **Open Access**

Elevated brain aluminium and early onset Alzheimer's disease in an individual occupationally exposed to aluminium: a case report

Mean Al content of frontal lobe tissue (n=46) is 2.98 (2.73) μgAl/g dry wt.

Range is 0.00 (less than the method blank) to 12.97 μgAl/g dry wt.

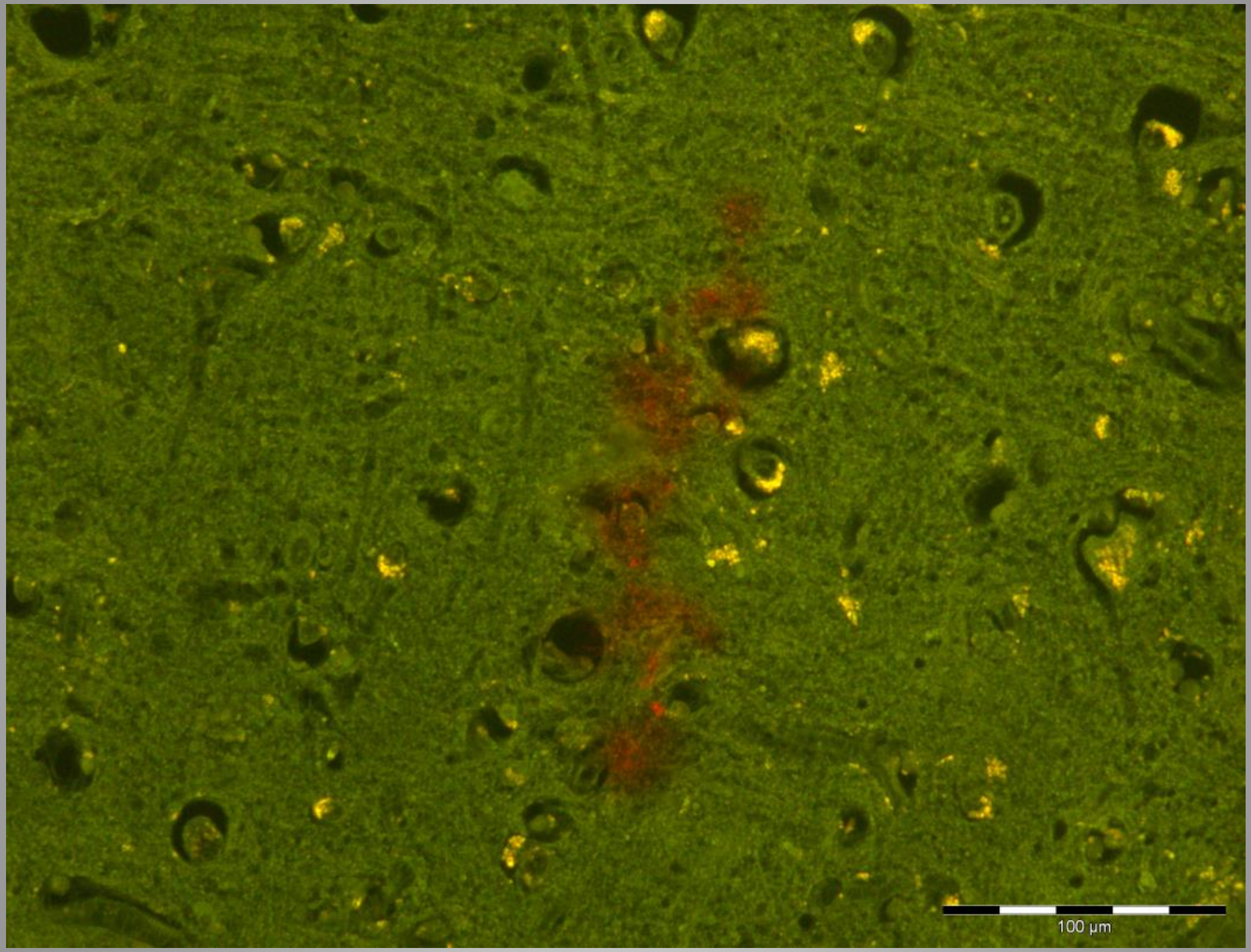
More than 30% of tissue samples had an Al content considered as pathological, greater than 3.50 μgAl/g dry wt.

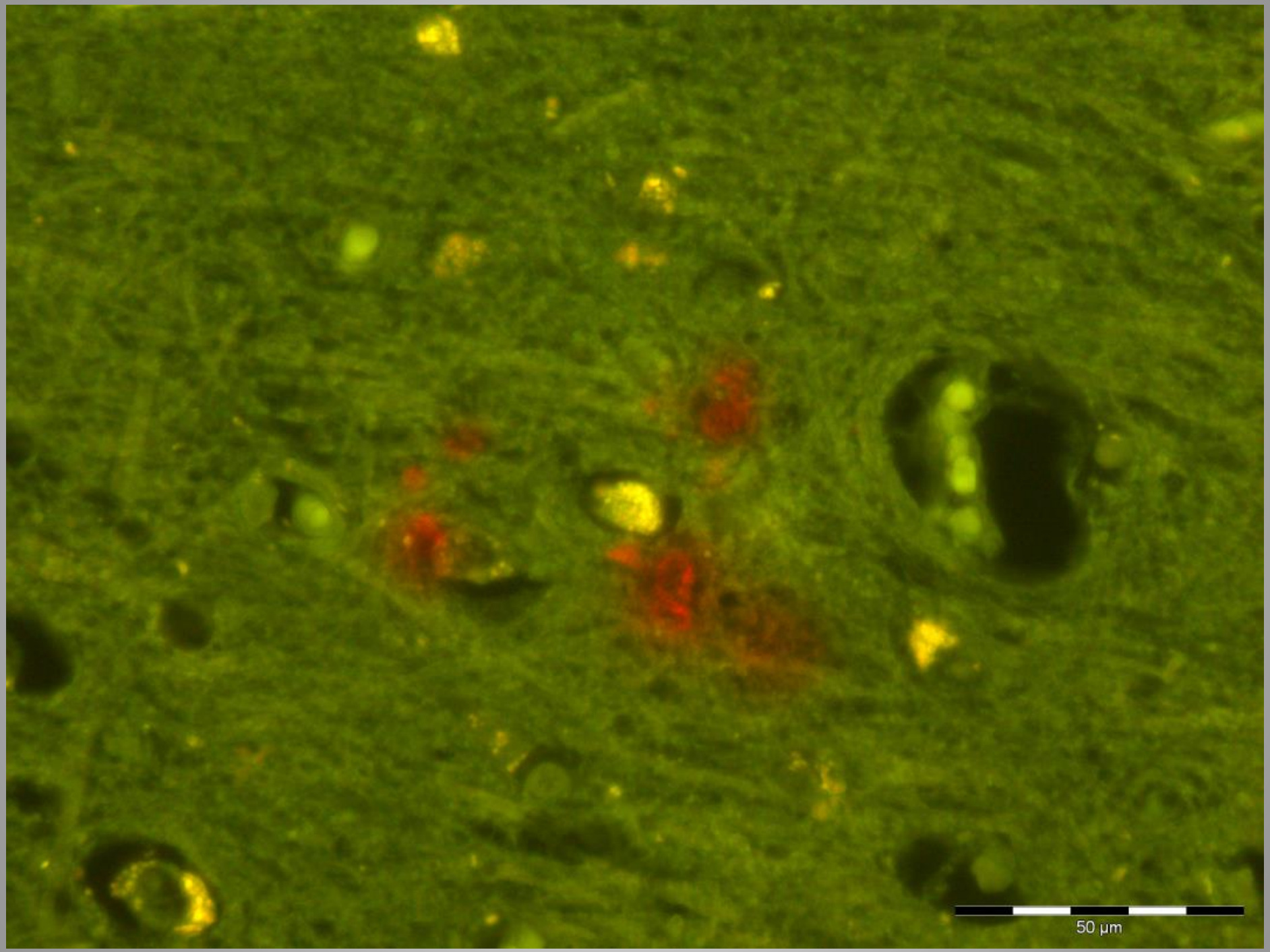
What about; Familial Alzheimer's Disease?

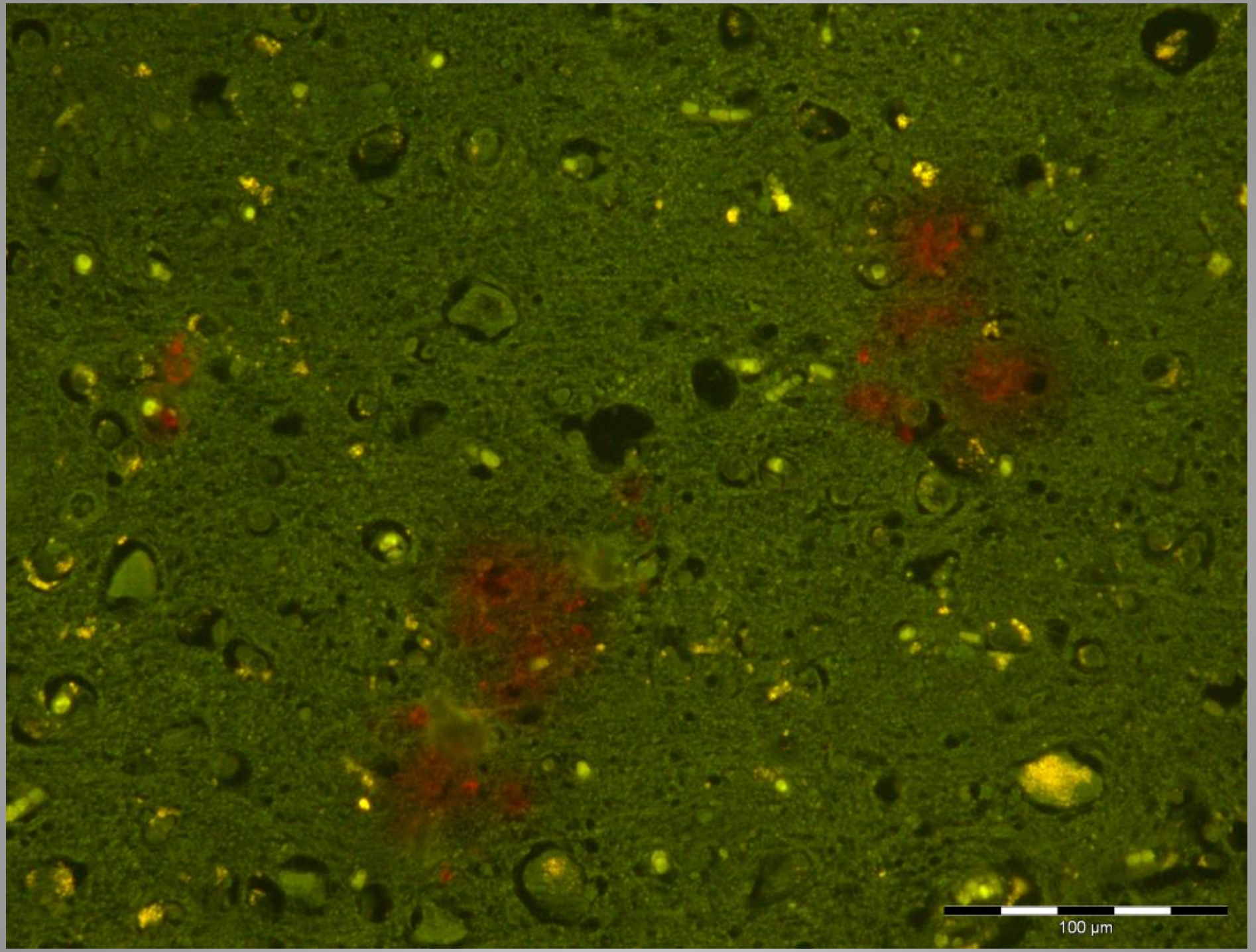
Summary indicating the lobe with the highest content of Al (Mean (SD) n=3)

(Pathologically Concerning/Pathologically Significant / 12 tissues)

Donor ID	Lobe	[Al] µg/g dry wt.
A1 0/0 /12	Frontal	0.44(0.31)
A2 0/4 /12	Occipital	9.99(1.61)
A3 6/3 /12	Occipital	4.29(3.21)
A4 3/2 /12	Parietal	3.30(4.43)
A5 1/2 /12	Frontal	7.05(6.10)
A6 1/3 /12	Occipital	9.57(14.08)
A7 2/0 /12	Temporal	1.81(0.78)
A8 3/6 /12	Frontal	14.41(18.44)
A9 4/2 /12	Frontal	3.81(4.11)
A10 5/1 /12	Occipital	2.97(1.01)
A11 2/2/12	Occipital	9.31(12.71)
A12 2/3 /12	Temporal	2.91(2.89)


100 µm


50 µm


100 µm

Complacency?
Aluminium in Drugs for Alzheimer's Disease

The Al content of Reminyl (Galantamine hydrobromide) is approximately 600 μg/g. When a single tablet is added to 50 mL of a simulated stomach solution (0.25% *w/v* sodium lauryl sulphate, 0.05% w/v sodium azide, 35mM sodium chloride, 5mL 15.8M HNO_3 and ultapure water, pH 1.5 – 1.7) and incubated for 1h at 37°C the tablet dissolves giving an orange solution*. The total [Al] of this solution is **1300.0 (76.7) μg/L (n=9).**

*Contains orange-yellow S-aluminium lake, E110

Multiple Sclerosis

ARTICLE *Multiple Sclerosis* 2006; **12**: 533–540

Elevated urinary excretion of aluminium and iron in multiple sclerosis

Christopher Exley[1], Godwin Mamutse[2], Olga Korchazhkina[3], Eleanor Pye[2], Stanislav Strekopytov[1], Anthony Polwart[4] and Clive Hawkins[2]

Study title:	**Urinary excretion of aluminium and silicon in secondary progressive multiple sclerosis.**
REC reference:	**14/YH/1115**
Amendment number:	**Substantial Amendment 1**
Amendment date:	**28 November 2014**
IRAS project ID:	**144340**

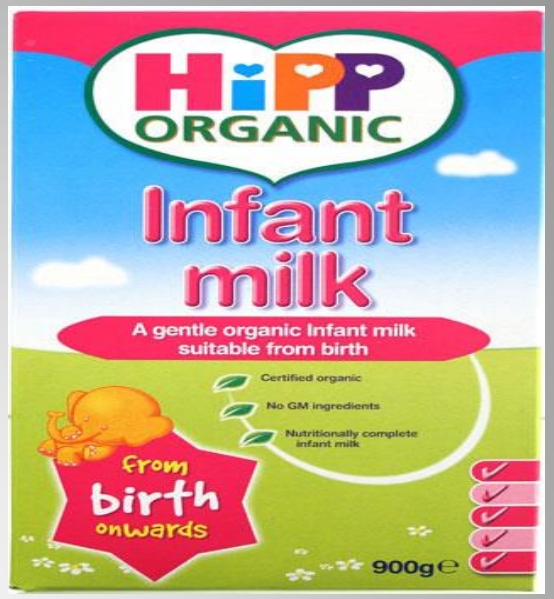
Study title:	**Urinary excretion of aluminium and silicon in secondary progressive multiple sclerosis.**
REC reference:	**14/YH/1115**
Amendment number:	**Substantial Amendment 1**
Amendment date:	**28 November 2014**
IRAS project ID:	**144340**

Primary objective – measurement of urinary excretion of aluminium, iron and silicon over two consecutive13 week periods to determine if the body burden of aluminium is influenced by drinking a silicon-rich mineral water.

Secondary objective – measurements of physical, cognitive and quality of life parameters in order to identify any clinical changes in SPMS patients.

Clinical trial complete and data are being processed, RESULTS ARE IMMINENT!

The Scandal of Infant Formulas!



Burrell S-A M and Exley C (2010) BMC Pediatrics 10:63
Chuchu N, Patel B, Sebastian B and Exley C (2013) BMC Pediatrics 13, 162.

Study title:	**The contribution of breast and formula feeding to the body burden of aluminium in infants (0-12 months)**
REC reference:	**14/WM/1114**
Amendment number:	**1**
Amendment date:	**09 December 2015**
IRAS project ID:	**148651**

Primary Objective: The research will monitor the urinary excretion of aluminium in term infants fed breast milk, infant formula and term infants fed combinations of the two over the first 12 months of their lives. Additional variables will include urine creatinine (Crt) and urinary excretion of silicon (Si).

The research will additionally monitor aluminium levels through the collection of hair samples as a secondary indicator. Both methods will be used for measurement of the body burden of aluminium in infants. The data collected will be then used to establish if there are any relationships between the body burden of aluminium and the type of infant feeding.

Aluminium Adjuvants in Vaccines and Immunotherapy

How Do They Really Work?!

There are no clinically-approved (aluminium) adjuvants!

There are only clinically-approved vaccines.

The safety of adjuvants is established alongside the safety of vaccines.

So, why are aluminium adjuvants used as placebos in vaccine trials?!

So, what do we know about aluminium adjuvants which are used in clinically-approved vaccines?

Aluminium oxyhydroxide (boehmite)

Poorly crystalline – hydrated structure (14.1% H_2O at the surface interface)

Composed of nanoneedles - 4.5 nm × 2.2 nm × 10 nm in size

Most frequently used adjuvant in commercial vaccines

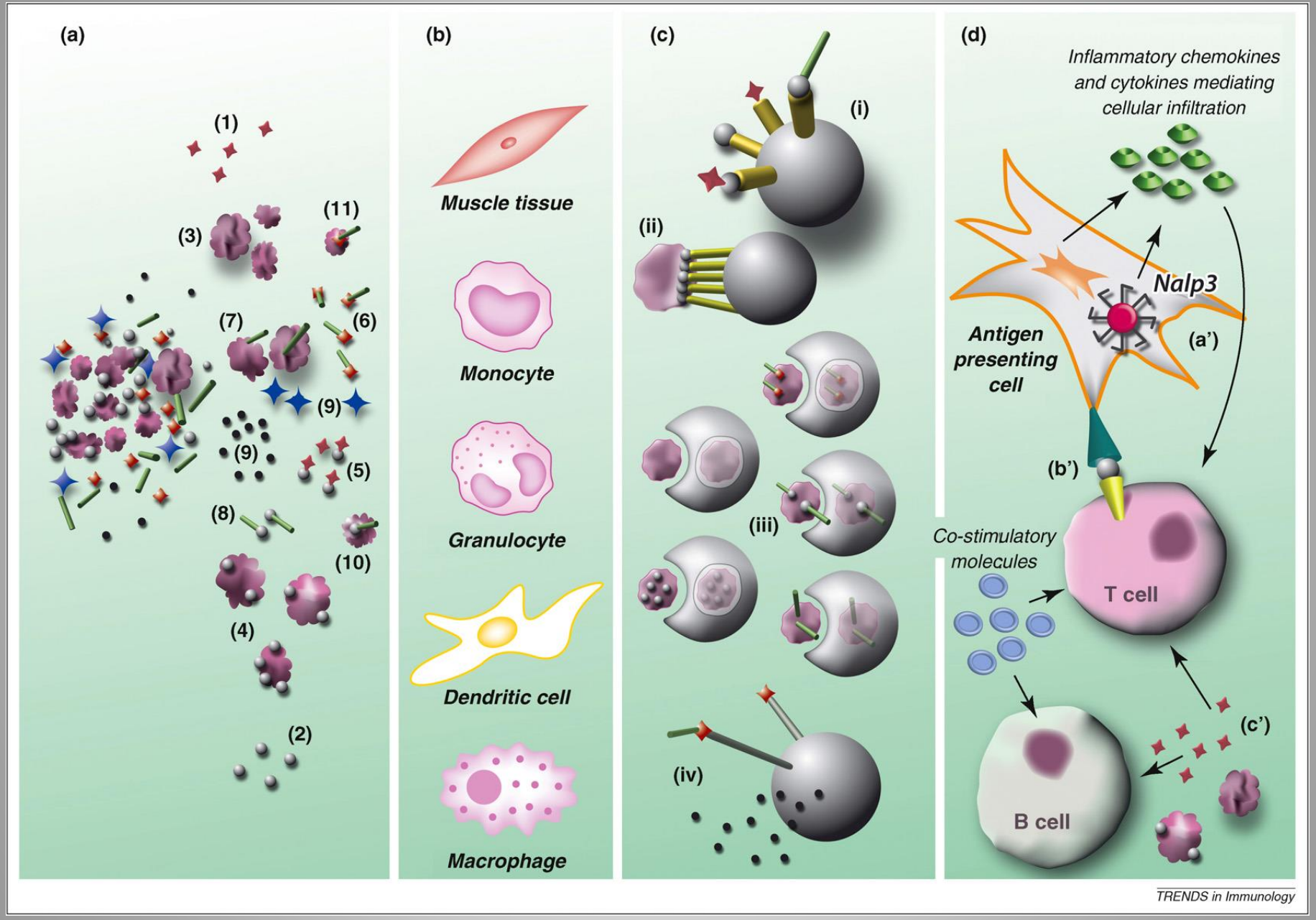
Aluminium hydroxyphosphate

Amorphous – hydrated structure (24.2% H_2O at the surface interface)

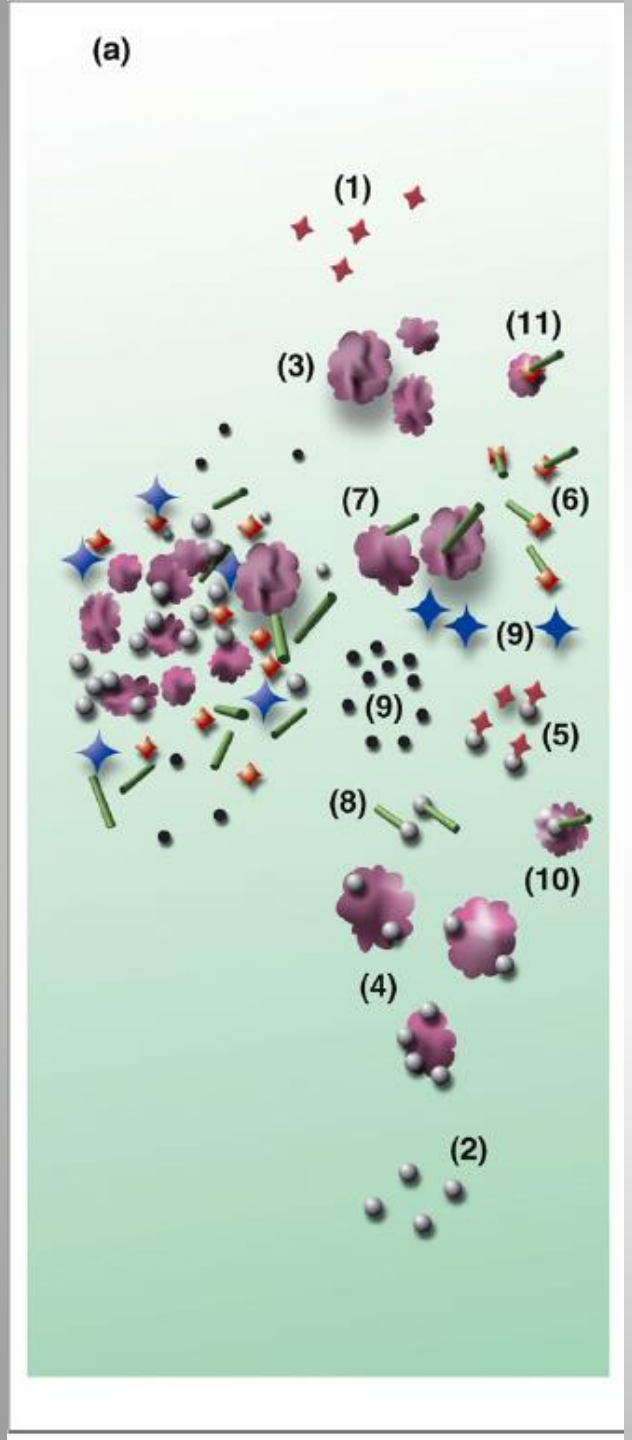
Composed of platy particles – 50nm in size

So, how do aluminium adjuvants work?

How might understanding this also begin to explain the known adverse events associated with their use in vaccines?



Exley et al.,(2010) The Immunobiology of aluminium adjuvants; how do they really work? Trends in Immunology, 31,103-109



The Critical Environment of the Injection Site

What Happens to the Aluminium Adjuvant?

Conclusions

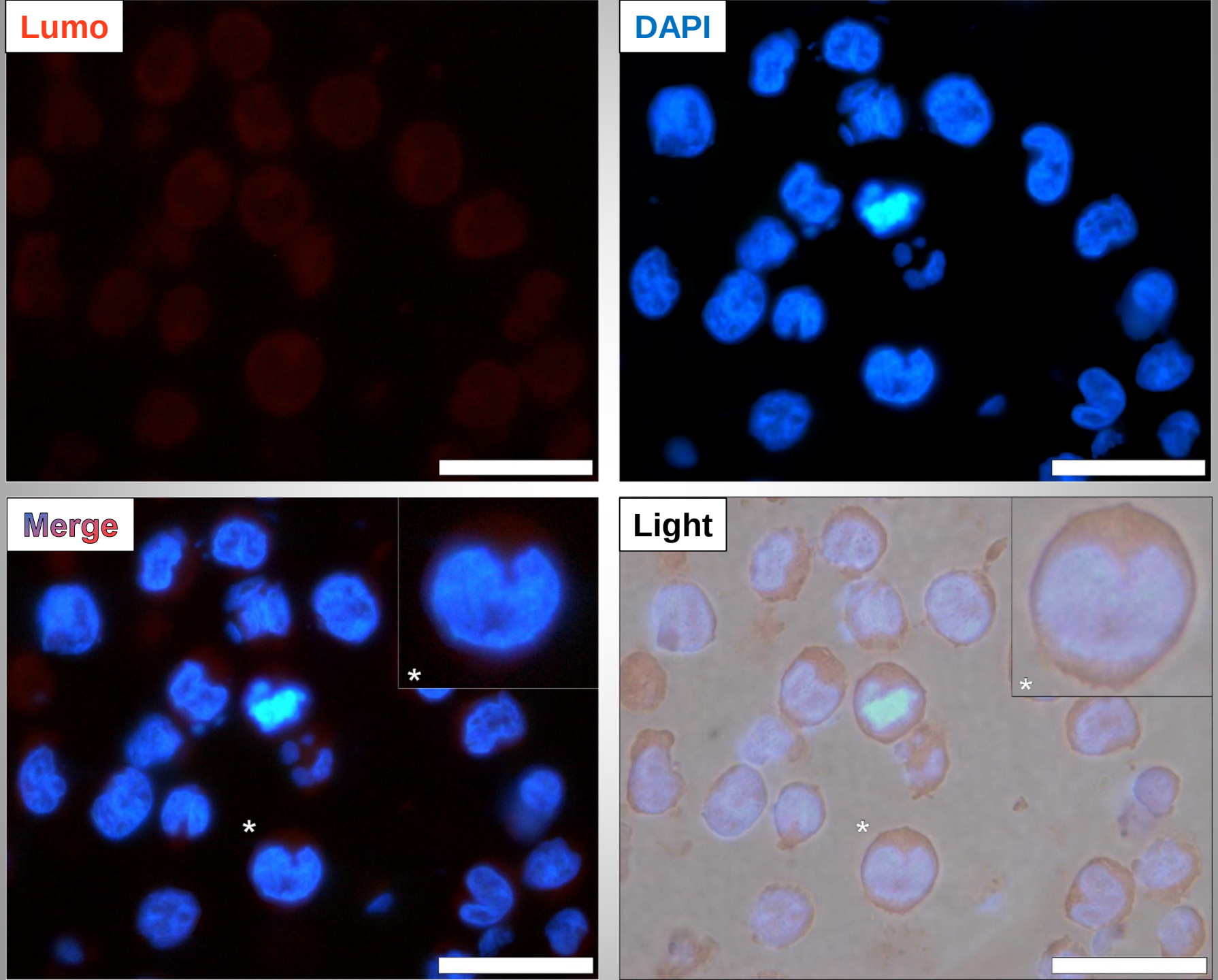
- In 0.9% NaCl, negatively charged Adju-Phos has a larger overall particle size than positively charged Alhydrogel
  - Alh - ~ 72% ≤ 2.7μm
  - Adj - ~ 28% ≤ 2.7μm

- At the site of injection both adjuvants become negatively charged upon administration

- Following administration Alhydrogel has a larger abundance of particles available for phagocytosis.
  - Alh - ~ 97% ≤ 2.7μm
  - Adj - ~ 20% ≤ 2.7μm

What About the Cellular Response to Aluminium Adjuvants?

Native THP-1 cells (R10)


Lumo
DAPI
Merge
Light
*
*
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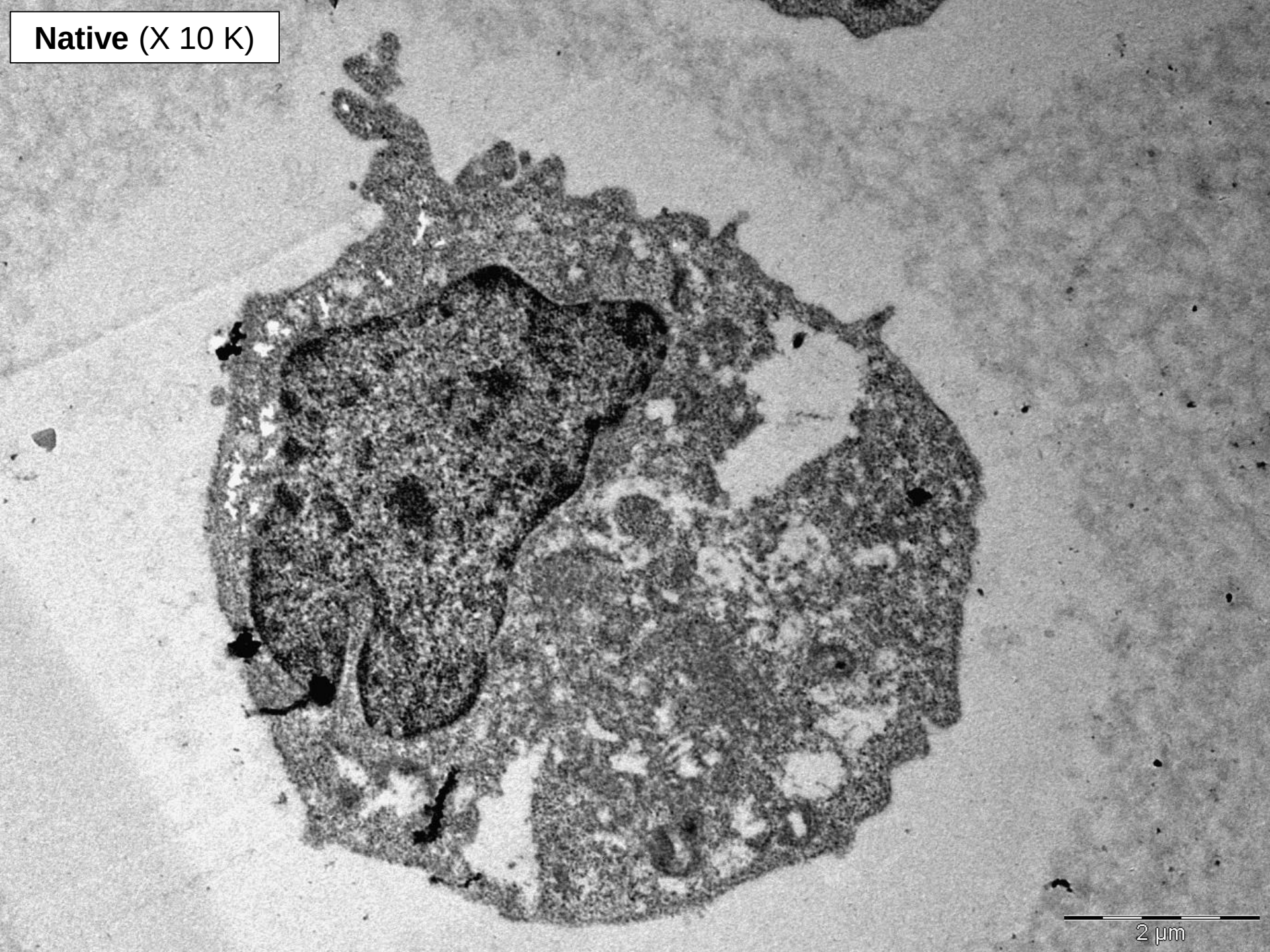
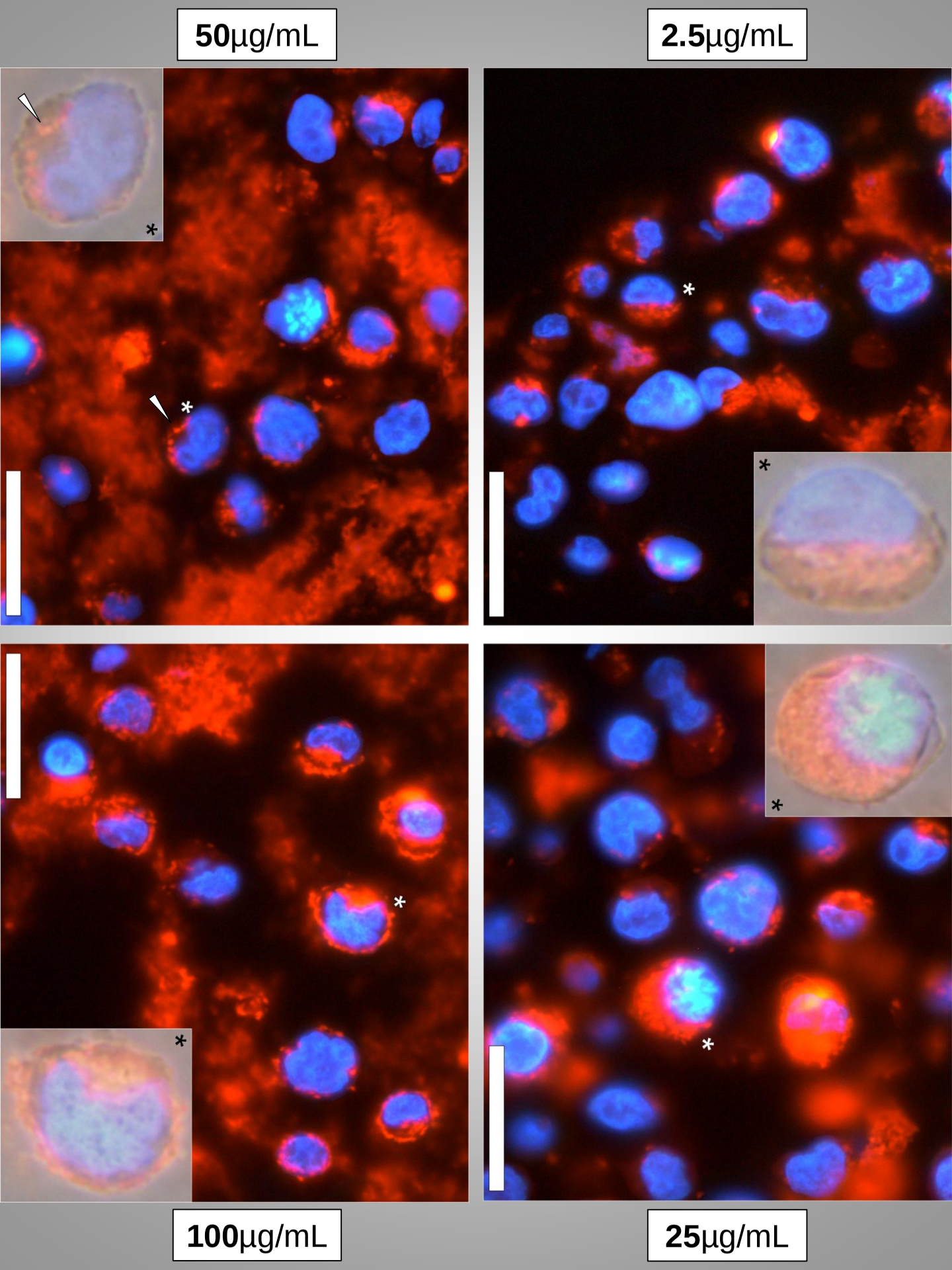
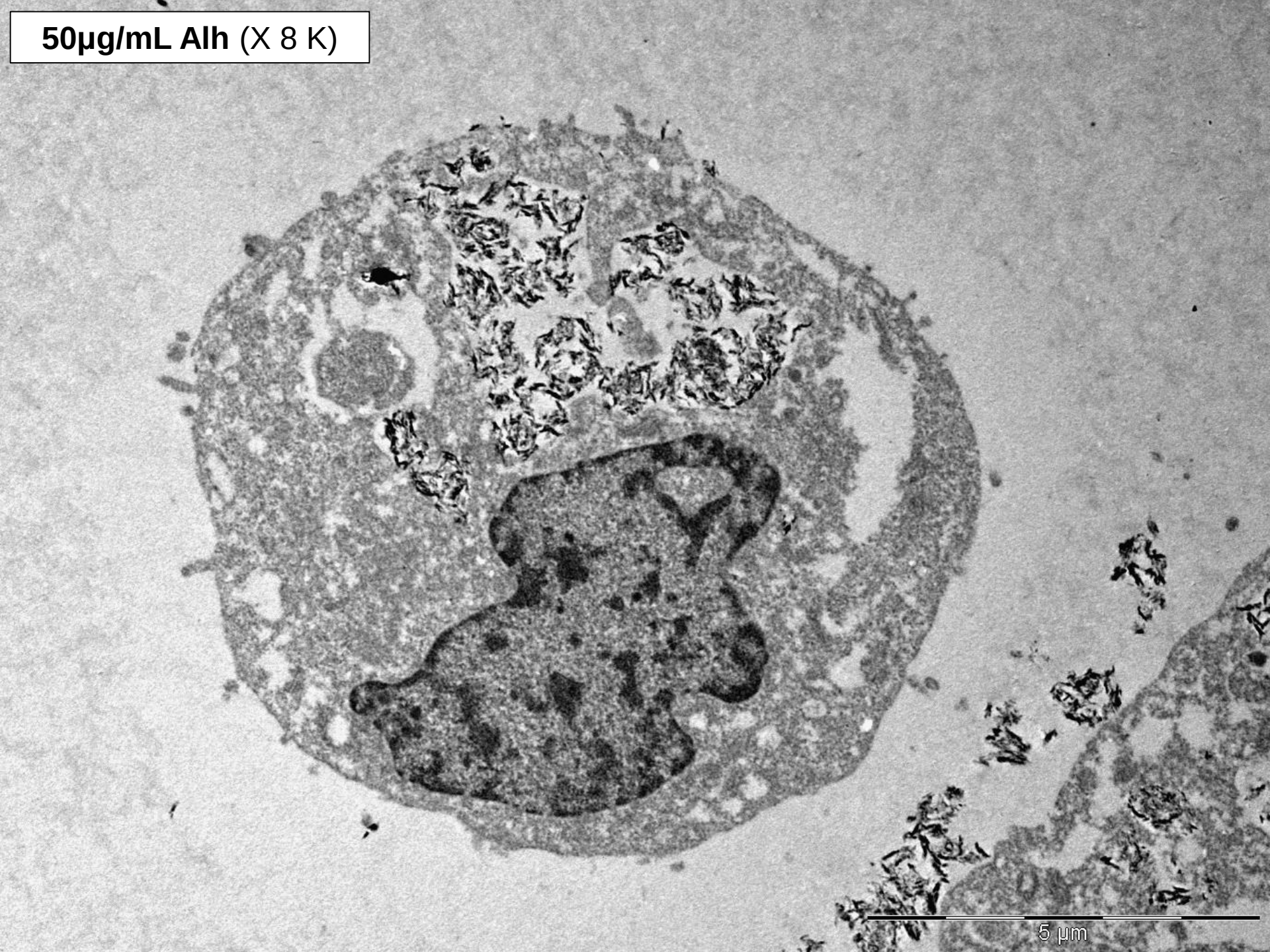
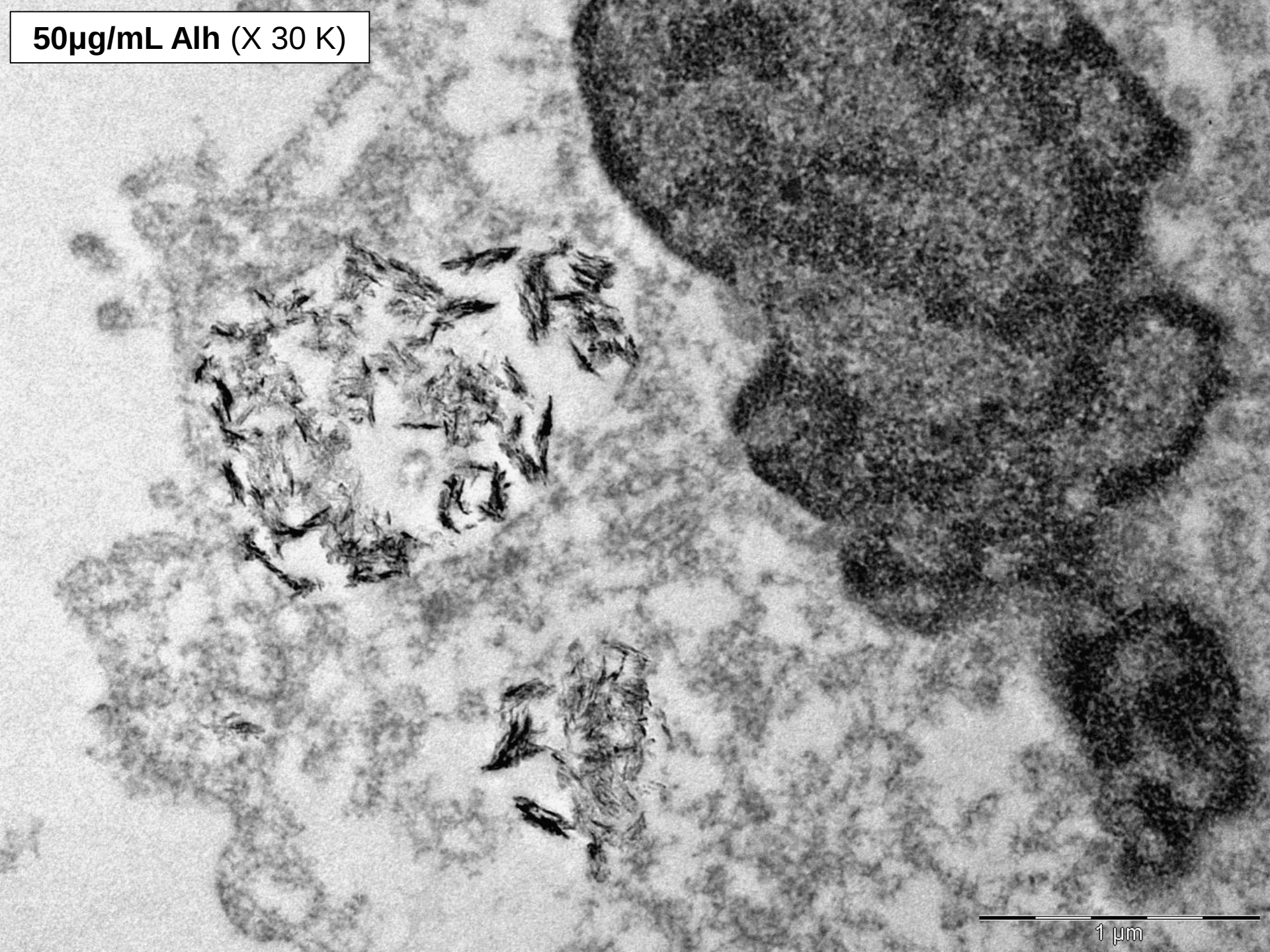

Native (X 10 K)
2 µm

Alhydrogel®

2.5 - 100 *µg/mL*

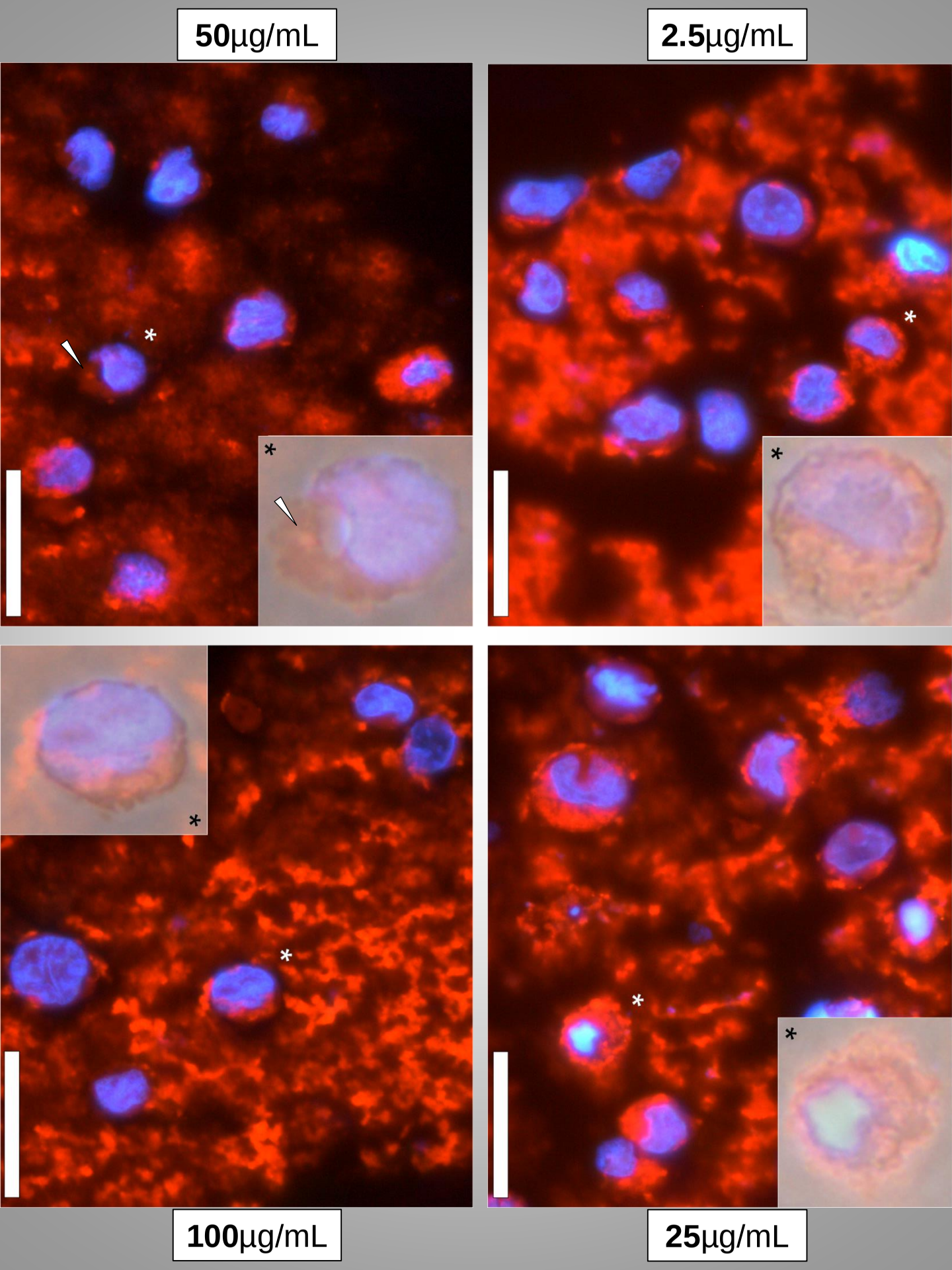

50µg/mL
2.5µg/mL
100µg/mL
25µg/mL

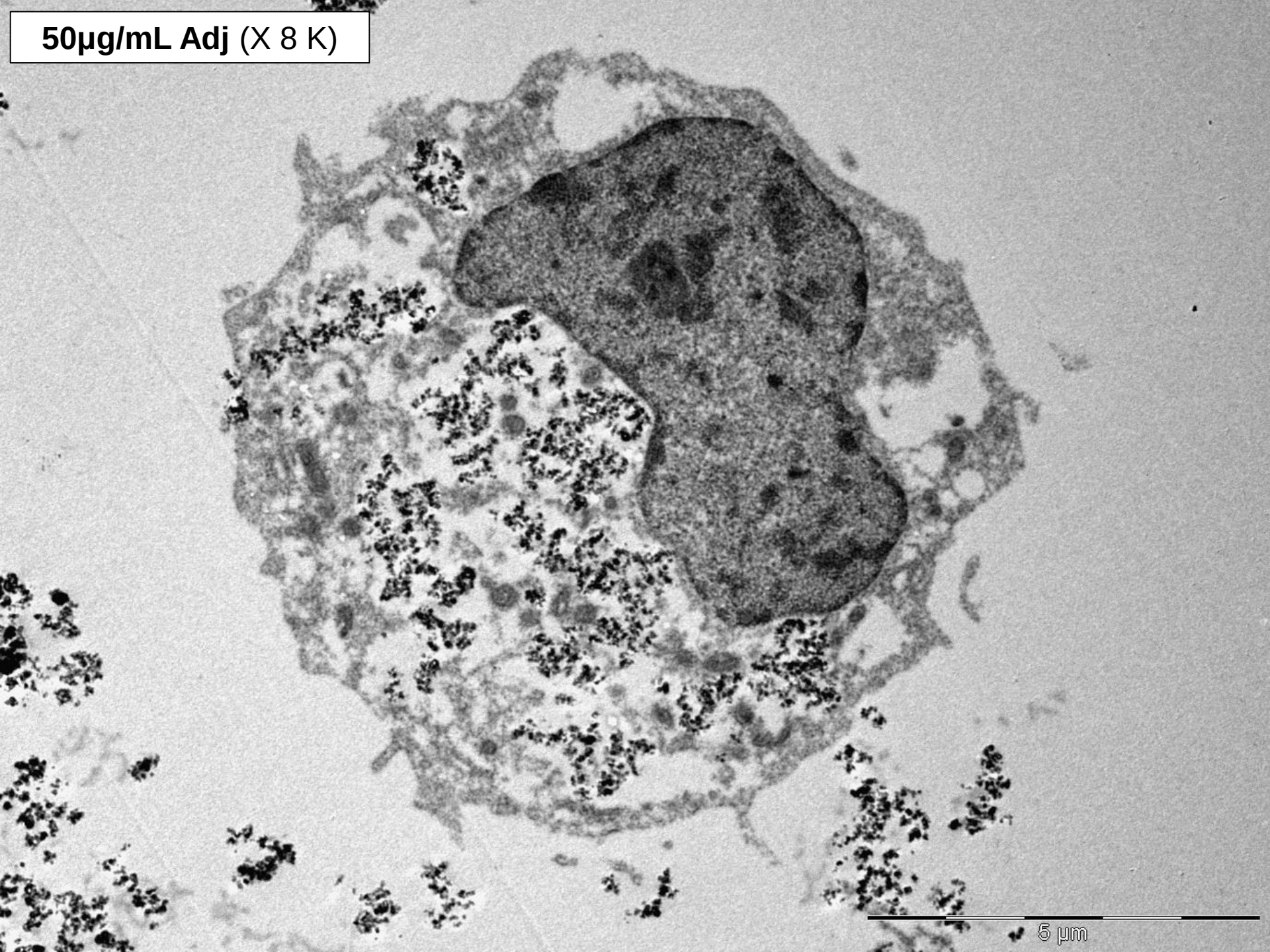

50µg/mL Alh (X 8 K)
5 µm

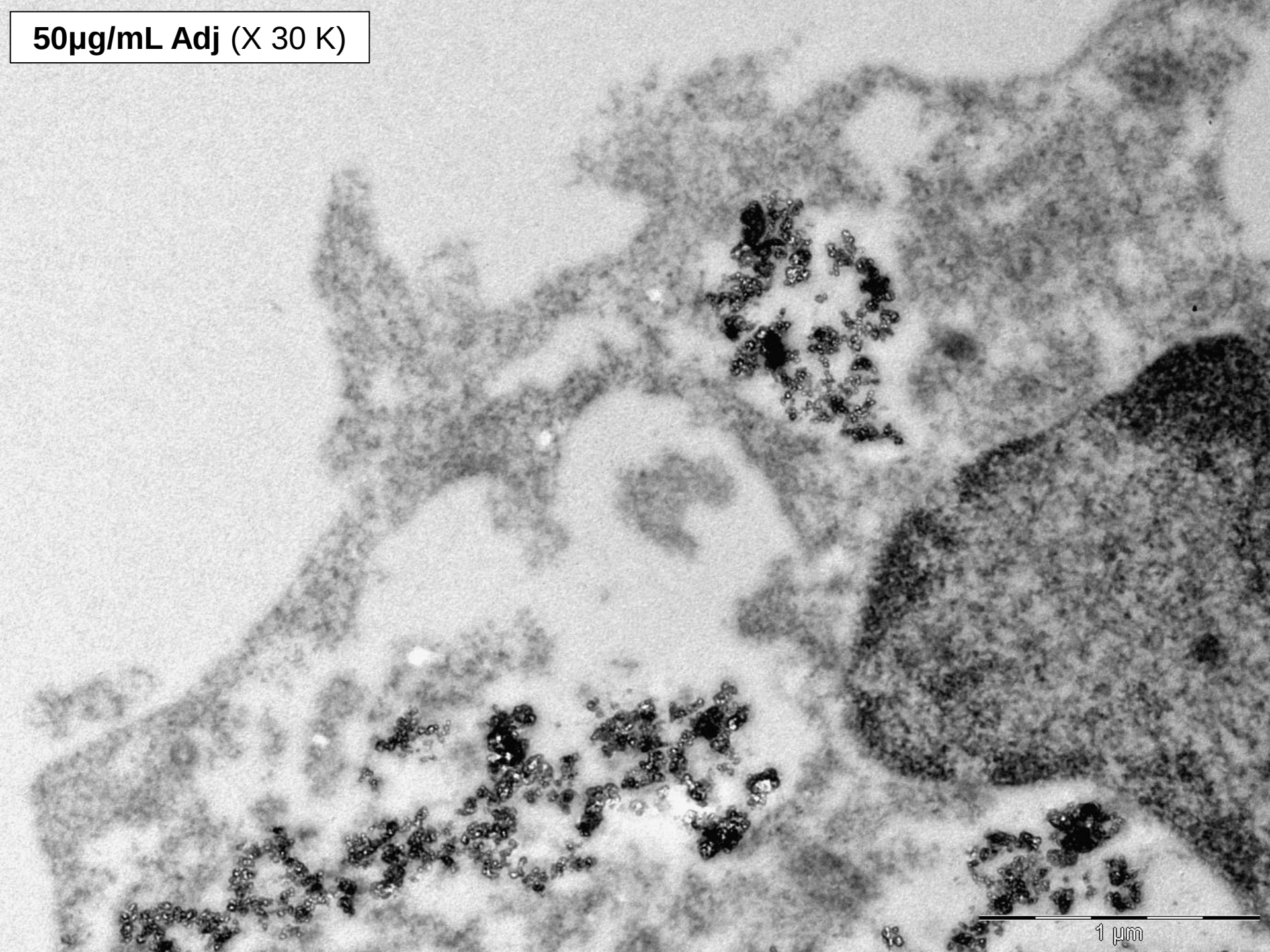

50µg/mL Alh (X 30 K)
1 µm

Adju-Phos®

2.5 - 100 *µg/mL*


50µg/mL
2.5µg/mL
100µg/mL
25µg/mL


50µg/mL Adj (X 8 K)
5 µm


50µg/mL Adj (X 30 K)
1 µm

So, What About the Toxicity of Aluminium Adjuvants?

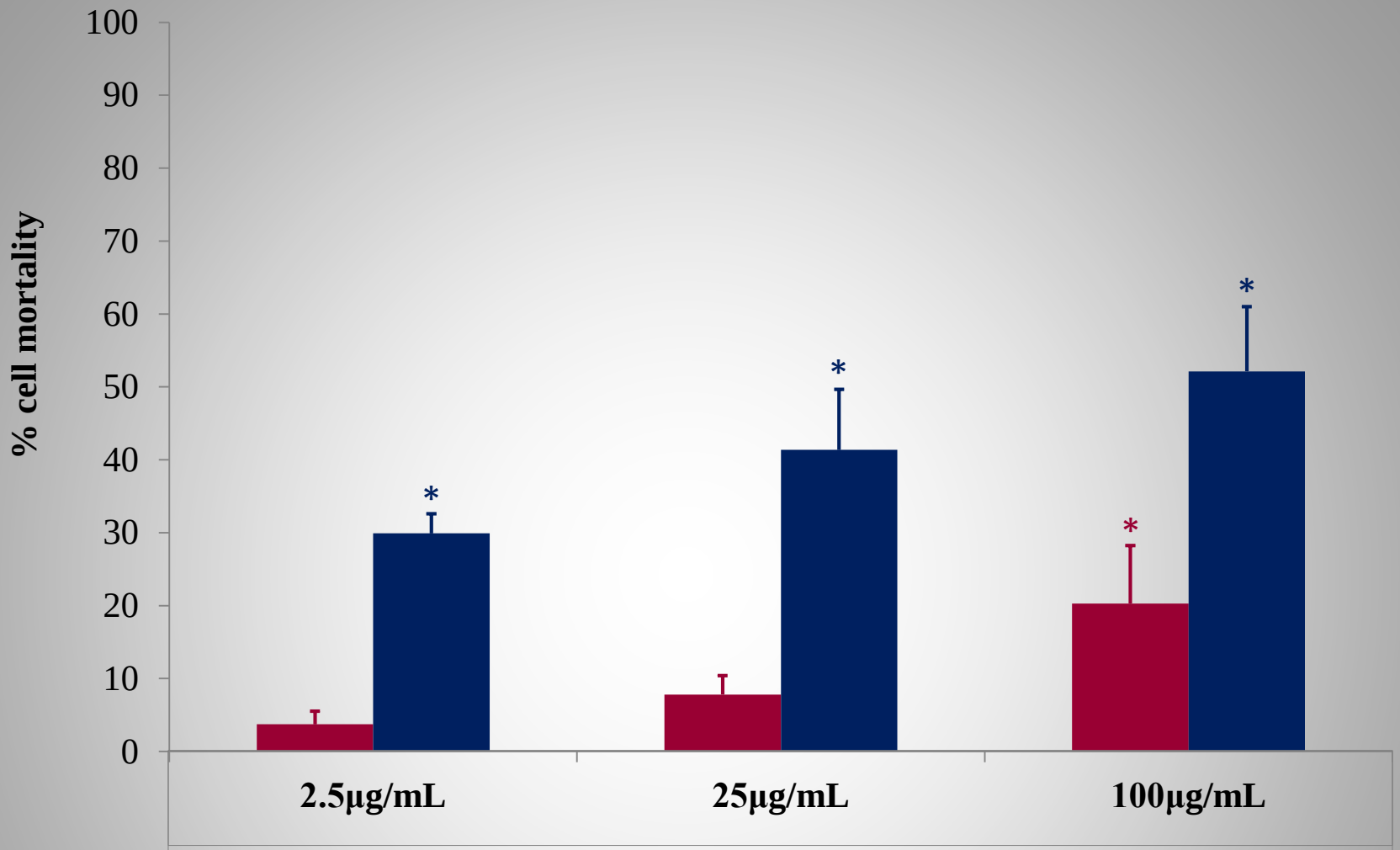


Fig 9: The % mortality experienced in THP-1 cell populations upon exposure to various concentrations of aluminium adjuvants relative to the control group, as elucidated using the live/dead cytotoxicity assay. Plum and blue bars represent Alhydrogel and Adju-Phos respectively. Error bars are representative of ±SD of 3 individual replicates and statistical significance is shown between treatments and respective control groups

Conclusions

- For the two aluminium adjuvants used in clinically approved vaccines, intracellular particulates of Alhydrogel® and Adju-Phos®, were observed localised in cell cytoplasm only.

- Only co-culture with Adju-Phos® resulted in the release of extracellular genetic material.

- The experimental Imject™ Alum adjuvant also exhibited particulates localised in the cell cytoplasm of THP-1 cells, typically larger in size.

Conclusions cont.

- Higher concentrations of aluminium adjuvants co-cultured with THP-1 cells were observed to result in their reduced cellular uptake (50 & 100µg/mL Adju-Phos® and 100µg/mL Imject™ Alum).

- The cytotoxicities of the two aluminium adjuvants used in clinically-approved vaccines are significantly different with Adju-Phos® expected to induce greater toxicity at the injection site.

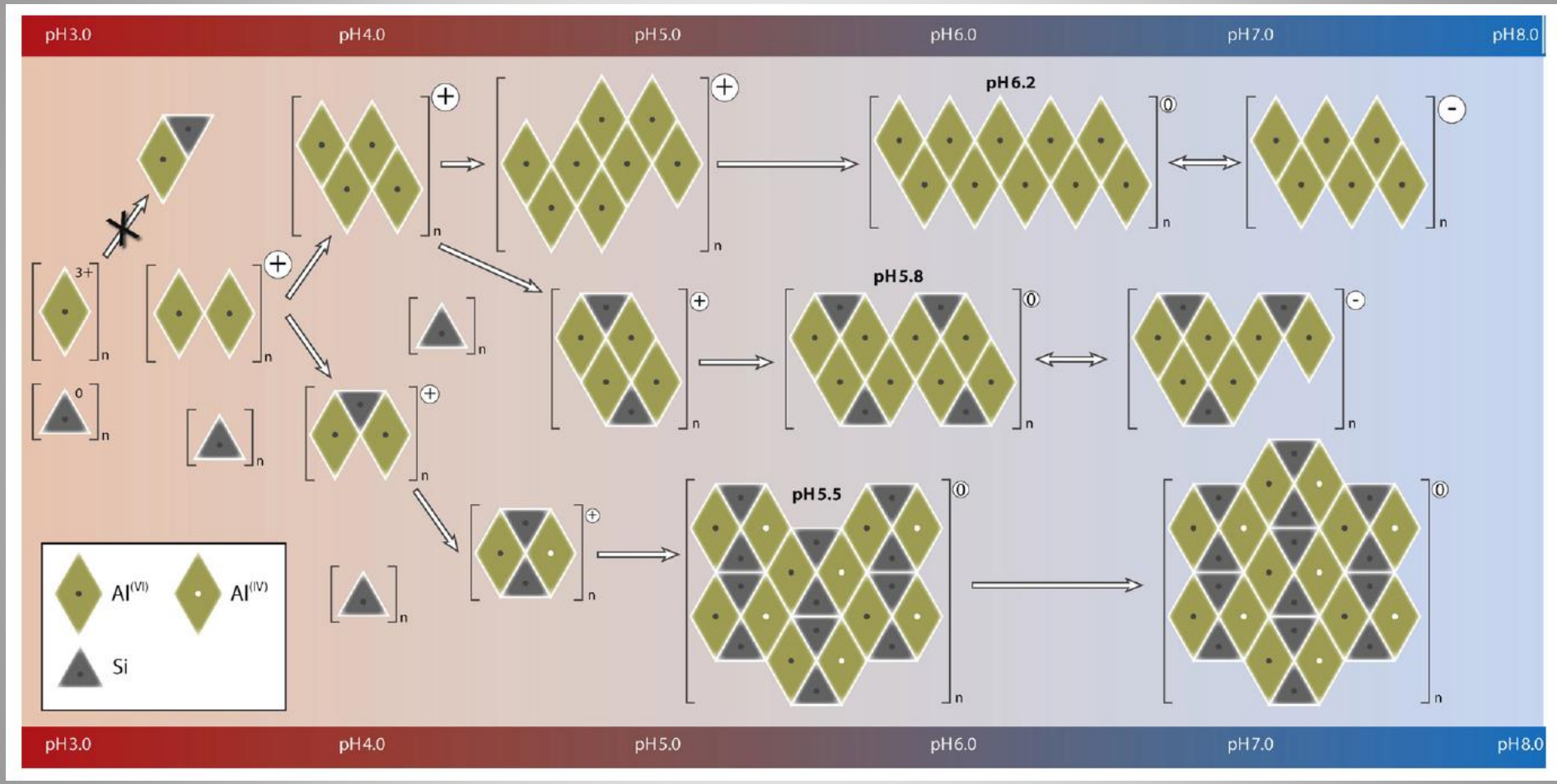
- The observed lower toxicity of Alhydrogel® despite its high intracellular burden may predispose this adjuvant to its translocation to sites away from the injection site.

Human Exposure to Aluminium

An Effective Therapeutic Strategy?


SPRITZER
Al MAN

The Unique Inorganic Chemistry of the Reaction of Aluminium with Silicic acid



Coordination Chemistry Reviews 256 (2012) 82–88

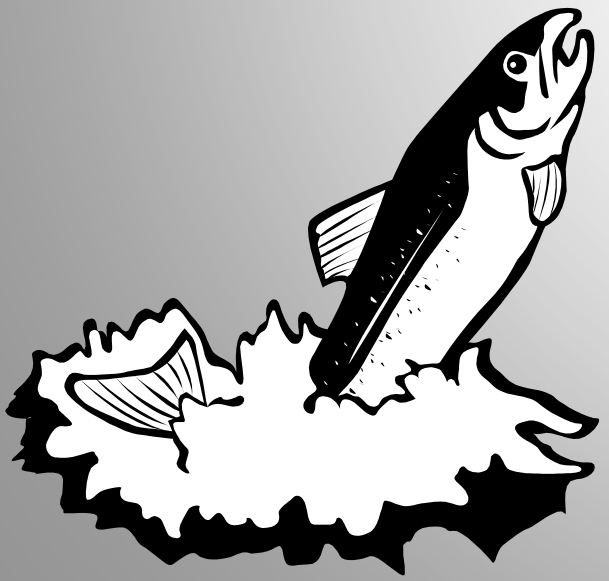
A Bioinorganic Solution to Aluminium-Related Disease?

1989

Acute toxicity of aluminium to fish eliminated in silicon-rich acid waters

J. D. BIRCHALL, C. EXLEY,
J.S. CHAPPELL & M. J. PHILLIPS

***Nature* 338, 146 - 148 (09 March 1989); doi:10.1038/338146a0**

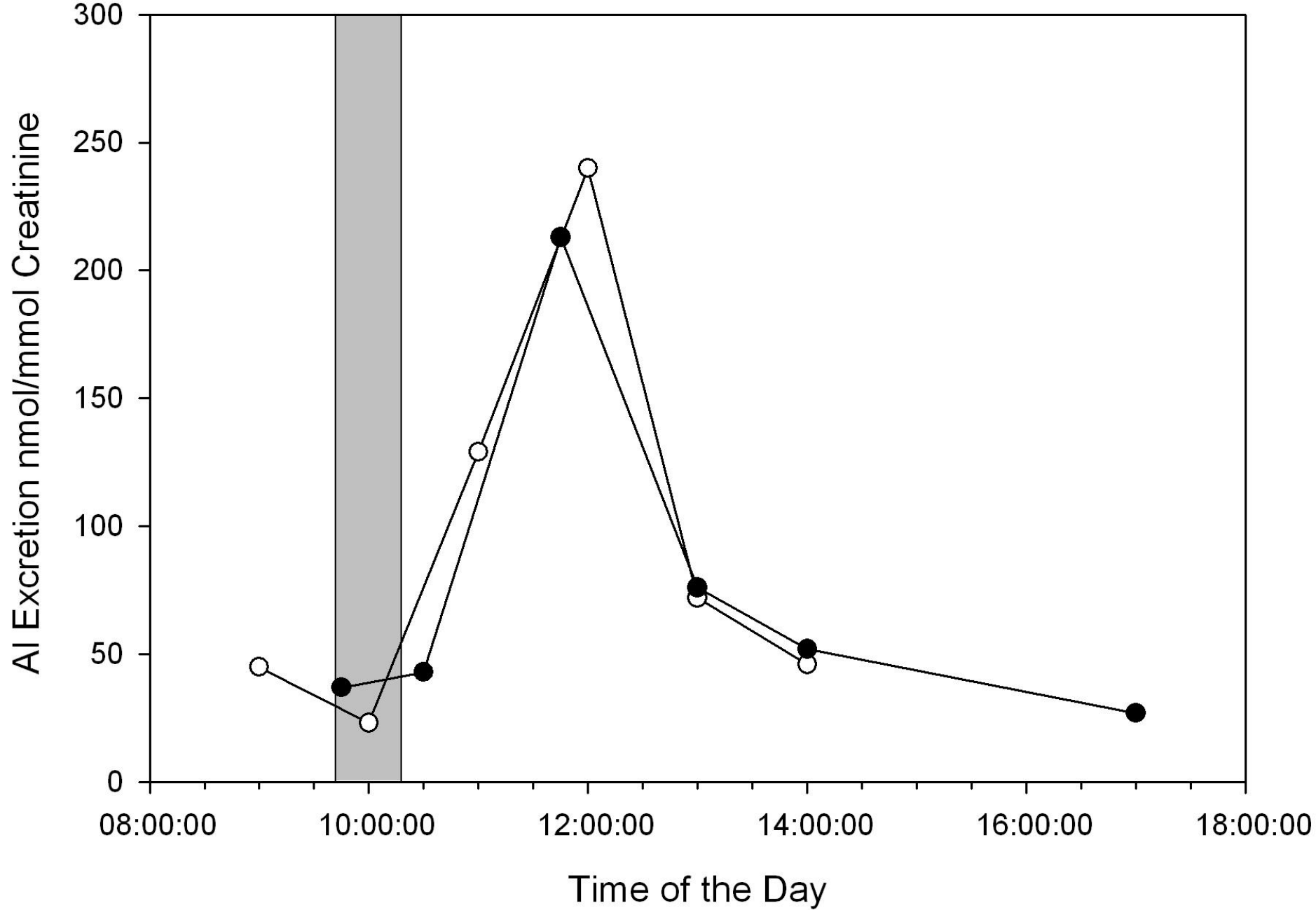


2006

Non-invasive therapy to reduce the body burden of aluminium in Alzheimer's disease

Christopher Exley, Olga Korchazhkina, Deborah Job, Stanislav Strekopytov, Anthony Polwart and Peter Crome

Journal of Alzheimer's Disease 10 (2006) 17–24


300
250
200
150
100
50
0
AI Excretion nmol/mmol Creatinine
08:00:00
10:00:00
12:00:00
14:00:00
16:00:00
18:00:00
Time of the Day

Ten individuals with Alzheimer's disease were asked to drink up to 1.5L of Volvic mineral water each day on five consecutive days as part of their everyday diets. The individuals were asked to collect their first urine sample of each day for both the five days preceding the trial (not drinking Volvic) and the five days of the trial.

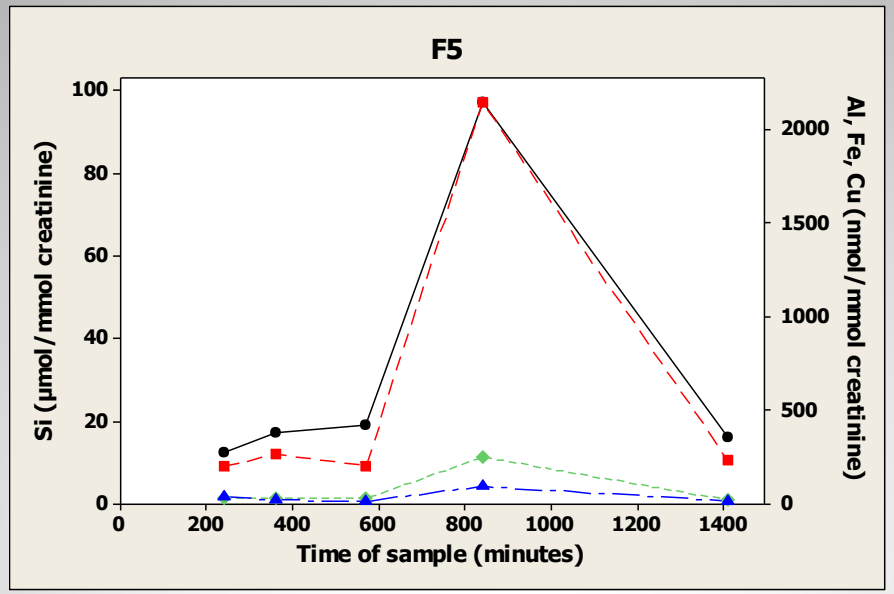
Urine samples, pre and post Volvic, were analysed for Al, Fe and Si.

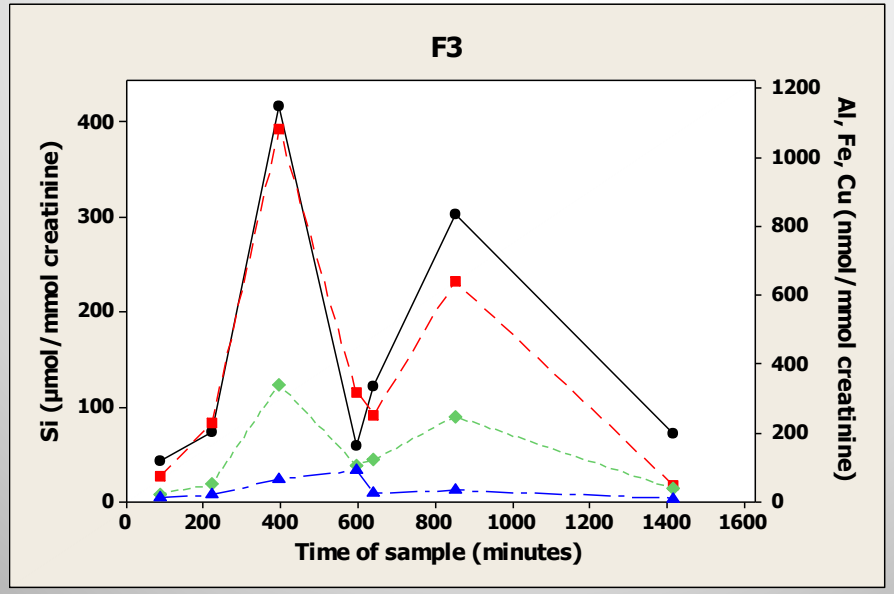
CONCLUSION

In individuals with Alzheimer's disease;

Drinking Volvic mineral water increased significantly ($P<0.001$) urinary excretion of silicic acid (34.3 ± 15.2 to 55.7 ± 14.2 μmol/mmol creatinine) and concomitantly reduced significantly ($P=0.037$) urinary excretion of aluminium (86.0 ± 24.3 to 62.2 ± 23.2 nmol/mmol creatinine). The latter was achieved without any significant ($P>0.05$) influence upon the urinary excretion of iron (20.7 ± 9.5 to 21.7 ± 13.8 nmol/mmol creatinine).

The reduction in urinary aluminium supported the future longer-term use of silicic acid as non-invasive therapy for reducing the body burden of aluminium in Alzheimer's disease.





Silicon
Aluminium
Iron
Copper

Journal of Alzheimer's Disease 33 (2013) 423–430
DOI 10.3233/JAD-2012-121231
IOS Press

Silicon-Rich Mineral Water as a Non-Invasive Test of the 'Aluminum Hypothesis' in Alzheimer's Disease

Samantha Davenward[a], Peter Bentham[b], Jan Wright[b], Peter Crome[c], Deborah Job[c], Anthony Polwart[d] and Christopher Exley[a,*]

[a]*The Birchall Centre, Lennard-Jones Laboratories, Keele University, Stoke-on-Trent, Staffordshire, UK*
[b]*Birmingham and Solihull Mental Health NHS Foundation Trust, The Barberry Centre, Birmingham, UK*
[c]*North Staffordshire Combined Healthcare NHS Trust, Harplands Hospital, Stoke-on-Trent, UK*
[d]*Life Sciences, Keele University, Stoke-on-Trent, Staffordshire, UK*

We have provided preliminary evidence that over 12 weeks of silicon-rich mineral water therapy the body burden of aluminium fell in individuals with Alzheimer's disease and, concomitantly, cognitive performance showed clinically relevant improvements in at least 3 out of 15 individuals.

The Twelfth Keele Meeting on Aluminium (Keele12)

4-8th March 2017

Pinnacle Hotel, Vancouver, Canada