



Impatto dei metalli pesanti sul sistema nervoso: dal neurosviluppo alle patologie neurodegenerative

Prof. Roberto Lucchini

Medicina del Lavoro, Università di Brescia

roberto.lucchini@unibs.it

Icahn School of Medicine at Mount Sinai, New York

roberto.lucchini@mssm.edu



Outline

1. Studi sui lavoratori
2. Parkinsonismo in provincia di Brescia
3. Adolescenti e anziani
4. Esposizione early life

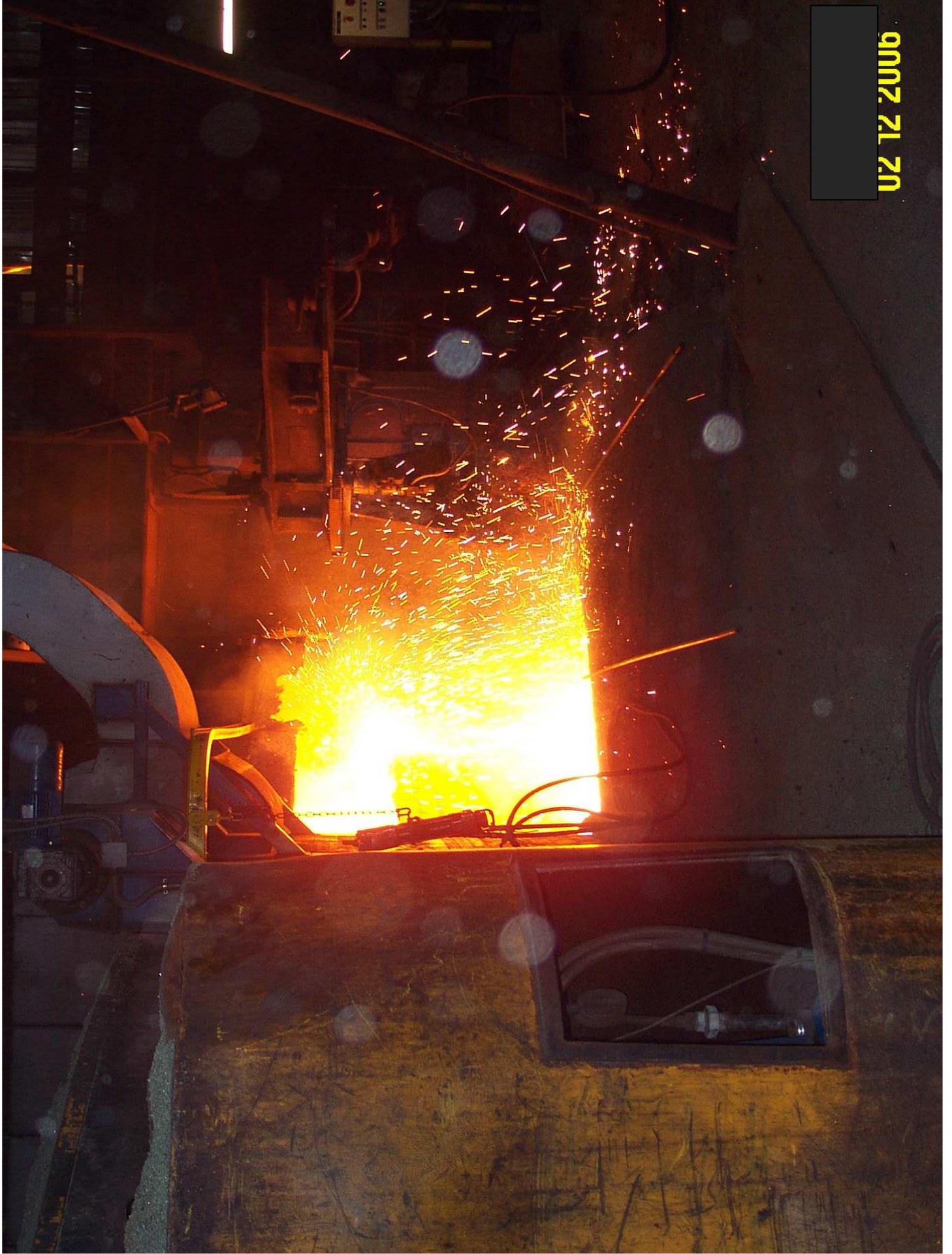
Occupational studies





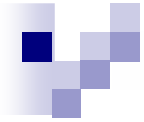
Ferroalloy production (Si-Mn, Fe-Mn, Fe-Cr)

Exposure \Rightarrow Mn (MnO_2 , Mn_3O_4), Fe, Pb, Zn, Cu, Cr, Cd



0902 21 20



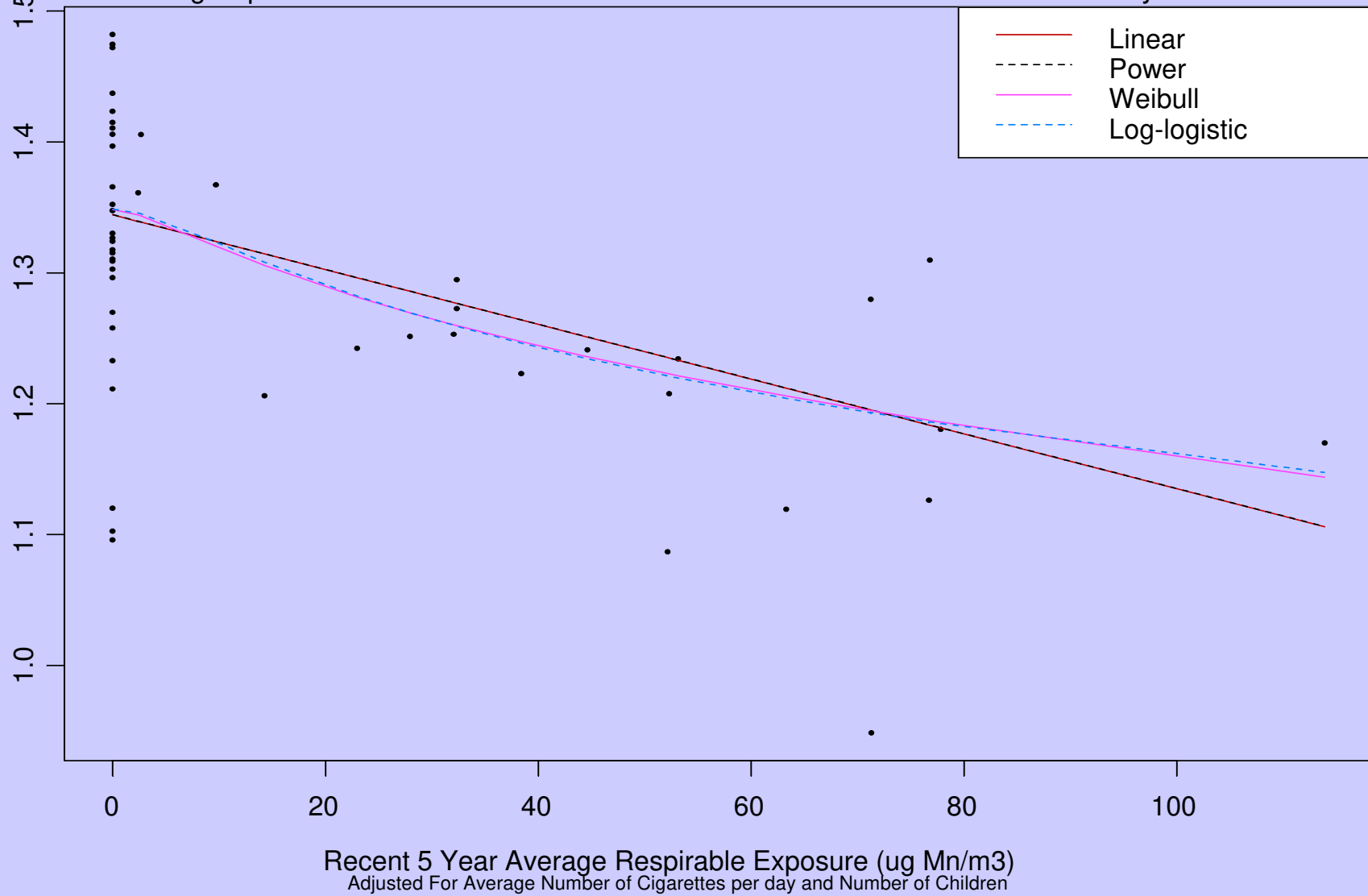


Luria Nebraska Motor Battery



Logarithm Base 10 Transform: LURIA - Thumb and Fingers Non-dominant

Figure 23: Dose Response Relationship between LURIA Thumb and Fingers and Exposure
Subgroup: Workers That Consume More Than 23.75 Grams Of Alcohol Per Day

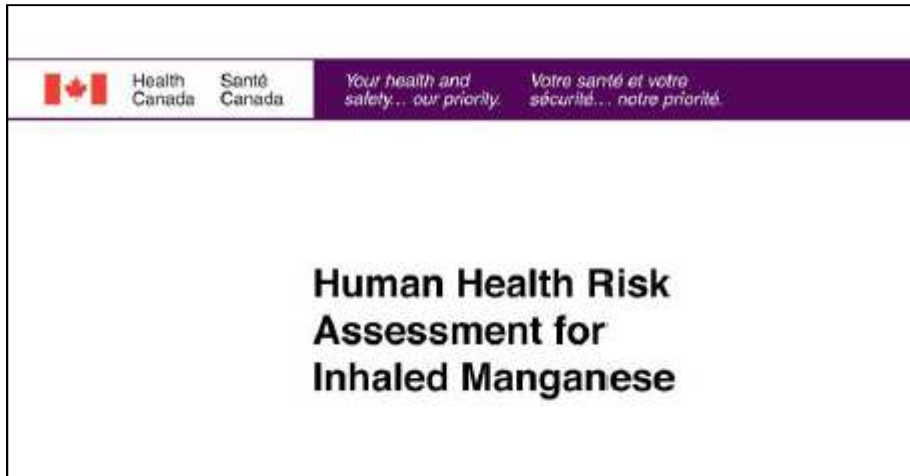


Lucchini et al. Long Term Exposure To “Low Levels” Of Manganese Oxides And Neurofunctional Changes In Ferroalloy Workers. Neurotoxicol, 1999; 20 (2-3): 287-298









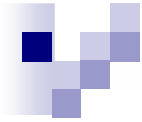
Neurotoxicology ® 20(2-3), 2897-298, 1999
Copyright © by Intox Press, Inc

Long Term Exposure to “Low Levels” of Manganese Oxides And Neurofunctional Changes in Ferroalloy Workers

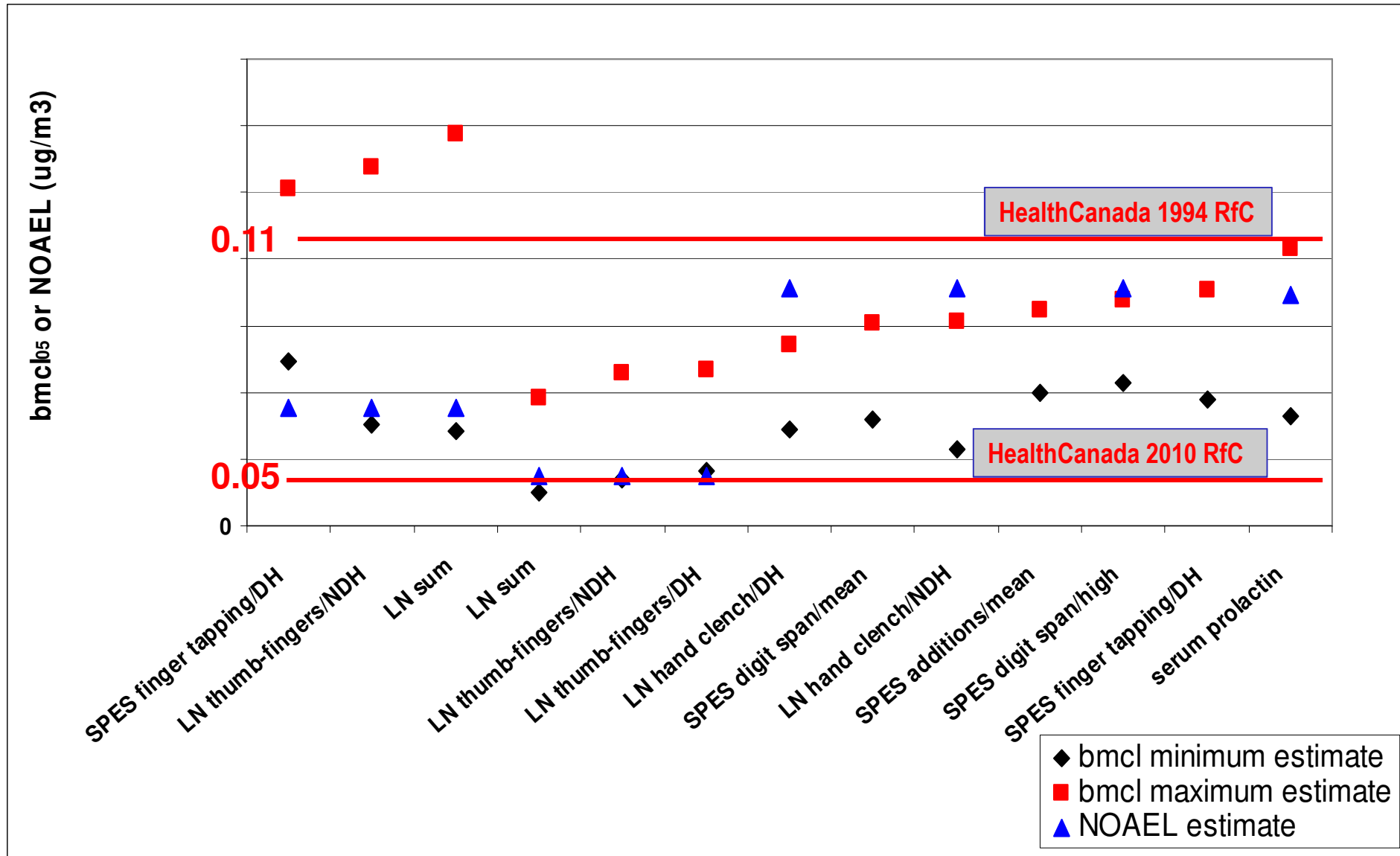
Roberto Lucchini, Pietro Apostoli, Carmine Perrone, Donatella Placidi, Elisa Albini, Piera Migliorati, Donna Mergler, Marie-Pascale Sassine, Silvana Palmi, Lorenzo Alessio



Canada



BMCL₀₅'s & NOAELs





Topics List

What's New List

Press release list

Environment Q & A

home

Guidance of the Ministry of the Environment

Policy areas and administrative activities

Environmental standards, laws and regulations

White paper, statistics and materials

Application and notification, public offering

Press and public relations

Press release

[home](#) > [Press and public relations](#) > [Press release](#) > Central Environment Council "About the way of hazardous air pollutants in the future (Tenth report)" for

2014 May 1,

Atmospheric environment

 Print this article

Central Environment Council "About the way of hazardous air pollutants in the future (Tenth report)" for

2014 April 18, held in the Central Environment Council air, noise and vibration Group: in (Chairman Kazuhiko Sakamoto Center for Environmental Science in Saitama-General), "About the way of hazardous air pollutants in the future (the first ten the following report)" is compiled, to the Minister of the environment from the central environment Council president in

+ **Guidance of the Ministry of the Environment**

+ **Policy areas and administrative activities**

+ **Environmental standards, laws and regulations**

+ **White paper,**

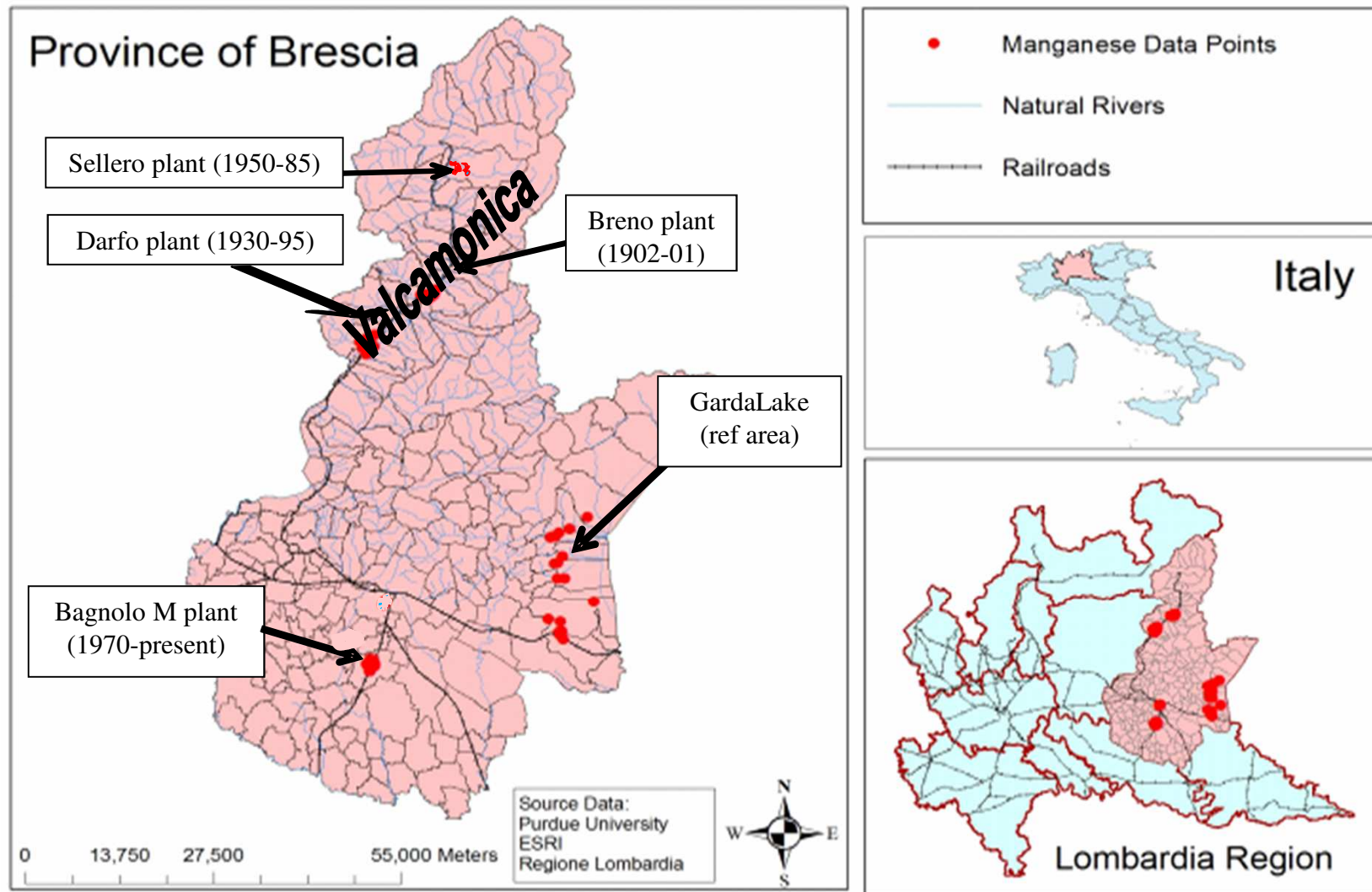
Prevalence of Parkinsonism

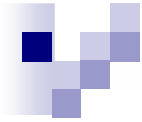




23 12 200

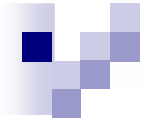
Mn exposure from ferroalloy emission



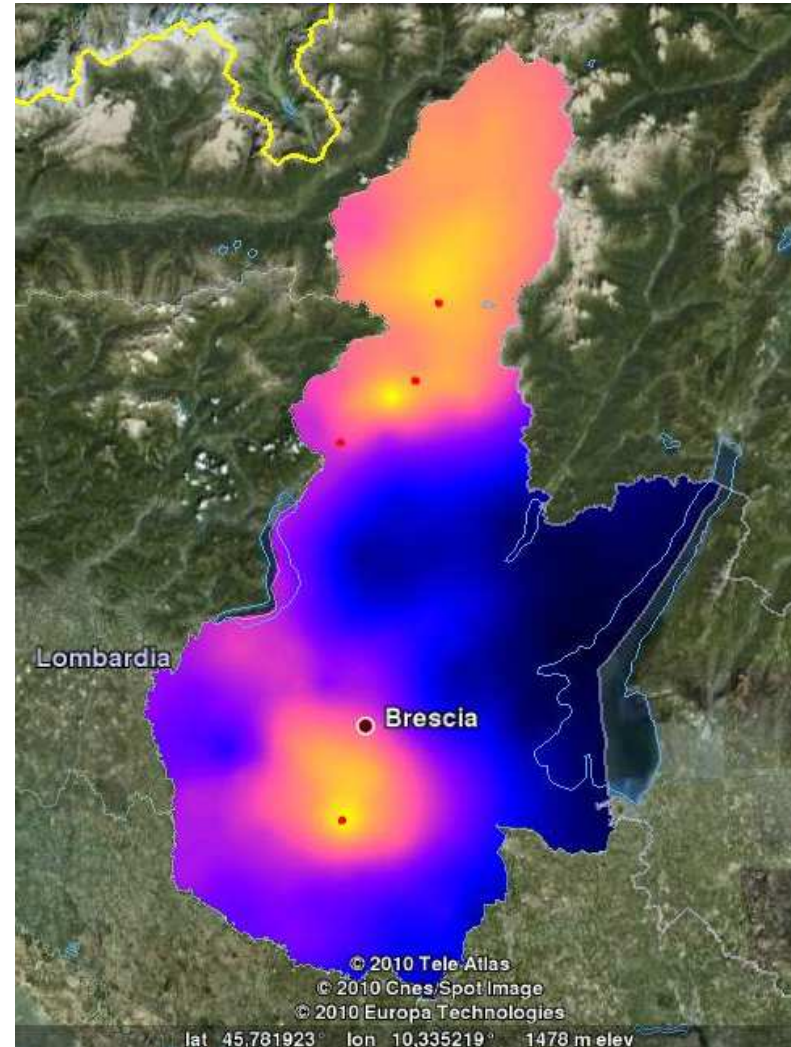
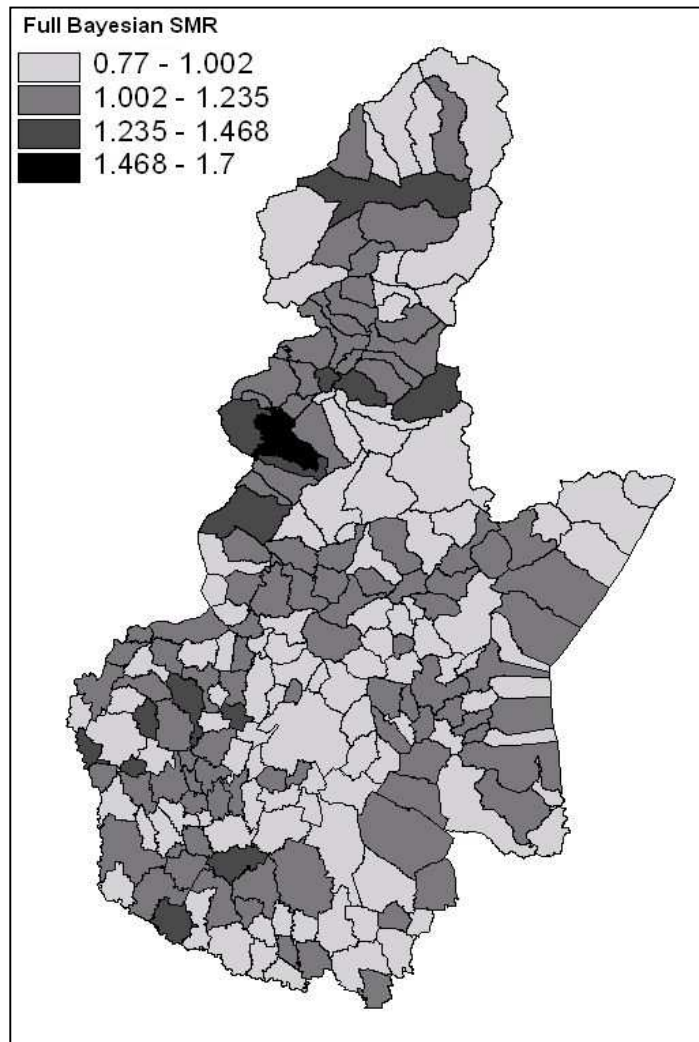


Study site	Cases	Population	Stand prev	Bayesian SMR
Valcamonica	324	77,708	492	1.25
Rest of the Province	2,353	826,289	321	1.00
Total Province	2,677	903,997	407	
Average ITA-EU			150	
SMR = 1.58; CI=1.41-1.76				

Lucchini et al., High Prevalence Of Parkinsonian Disorders Associated To Manganese Exposure In The Vicinities Of Ferroalloy Industries.
Am J Ind Med 2007; 50: 11: 788-800



SMR Parkinsonism vs. Mn in dust $p=0.005$



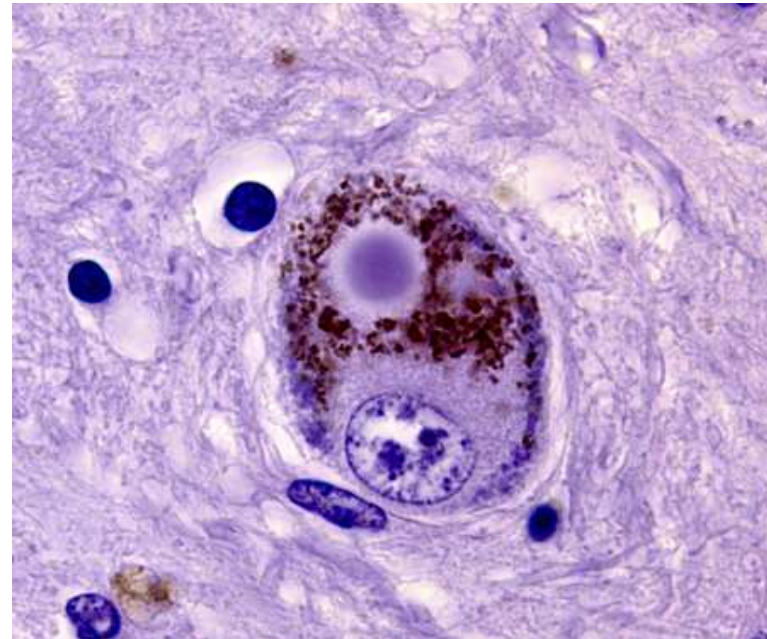
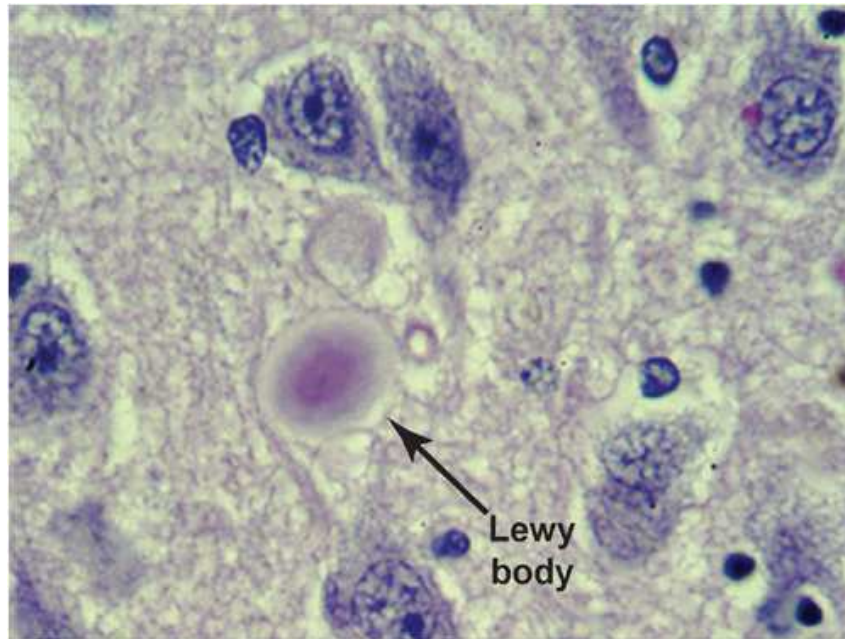


Parkinson's Disease

Pathological hallmarks:

1. degeneration of dopaminergic neurons of **pars compacta of the substantia nigra**
2. accumulation of **alpha-synuclein protein** in the form of Lewy bodies

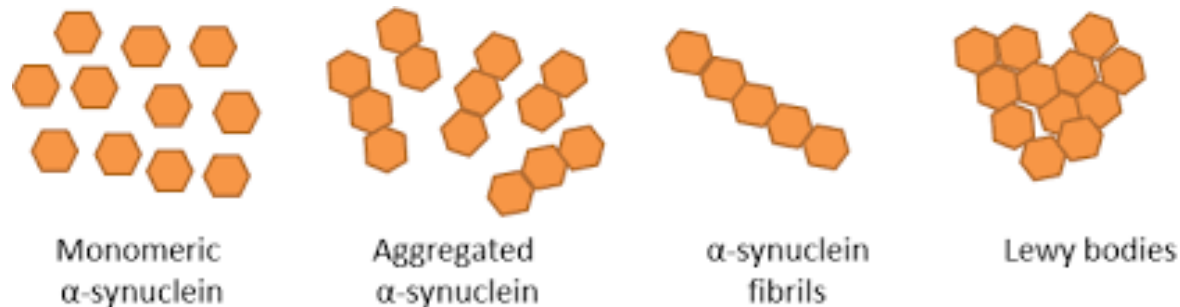
Fibrils of α -synuclein deposited in the neuronal body form round lamellated eosinophilic cytoplasmic inclusions, **Lewy bodies** cause neuronal degeneration and death



Metals and alpha-synuclein

Physiologically poorly structured “unfolded protein” → fibril formation → LB

Al(III), Cu(II), Cd(II) Fe(III) induce fibrils through protein oxidation by ROS formation

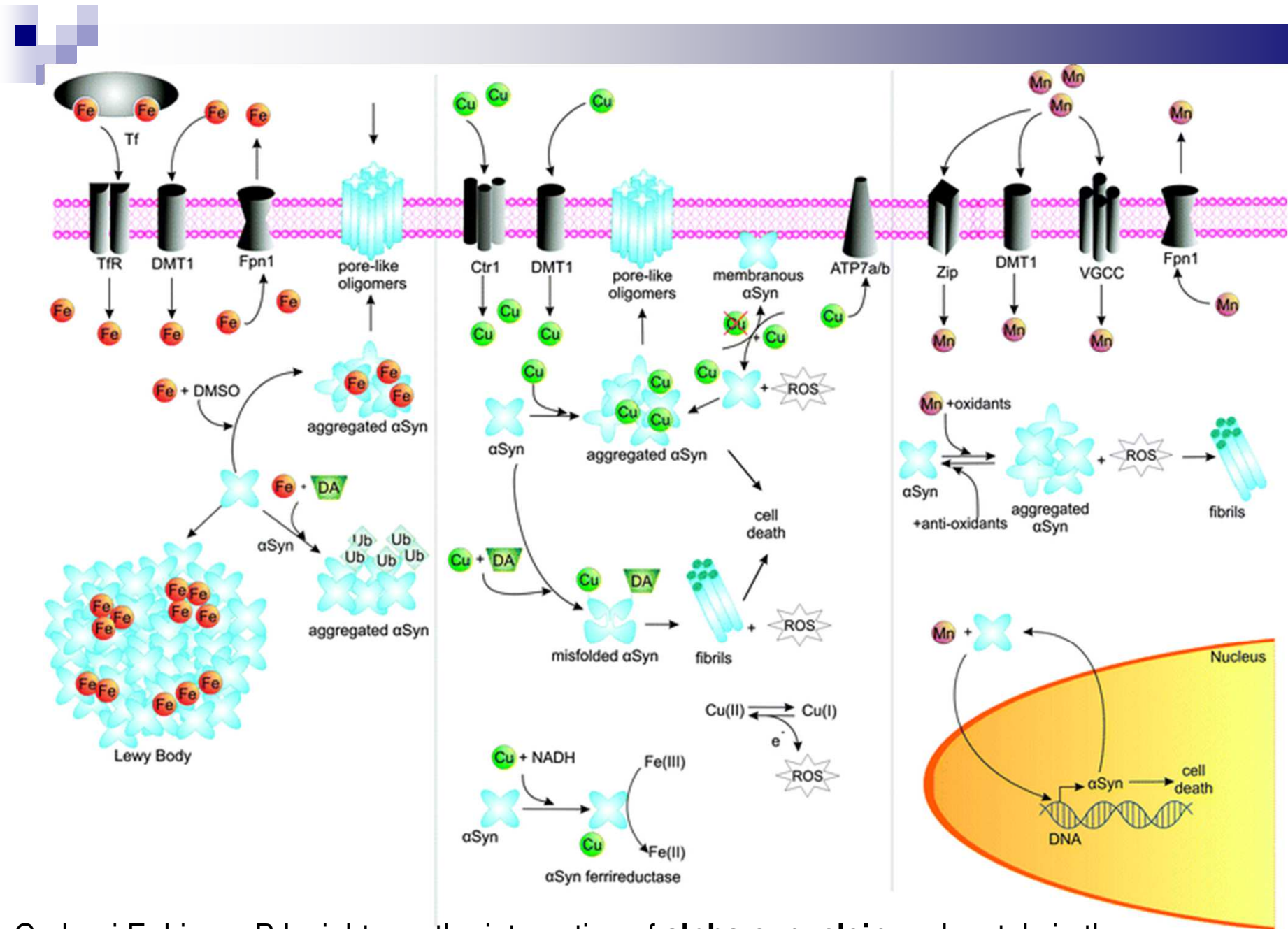




PD case control

Variables	OR (IC 95%)
Agecat (65,72)	1,49 (0,97 - 2,3)
Agecat (72,78)	2,11 (1,33 - 3,35)
Agecat (78,97)	2,44 (1,52 - 3,9)
Sex (M vs F)	1,04 (0,74 - 1,48)
Smoking (yes vs never)	0,76 (0,54 - 1,06)
Parents with PD	4,75 (2,61 - 8,63)
SNCA (TC vs TT)	1,36 (0,96 - 1,92)
SNCA (CC vs TT)	2,27 (1,41 - 3,66)
Metals exposure	2,25 (1,26 - 4,02)
Pesticides exposure	0,48 (0,09 - 2,65)
Born in the province of Brescia	1,62 (0,97 - 2,72)

(Preliminary unpublished data)



Carboni E, Lingor P Insights on the interaction of **alpha-synuclein** and metals in the pathophysiology of Parkinson's disease. *Metallomics*. 2015 Mar;7(3):395-404.

Community studies

The PHIME Network

Public Health Impact of Metal Exposure



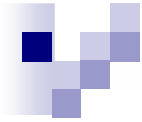
- 720 adolescents aged 11-21 yrs
- 255 elderly aged 60-75 yrs
- 30 pregnant women pilot



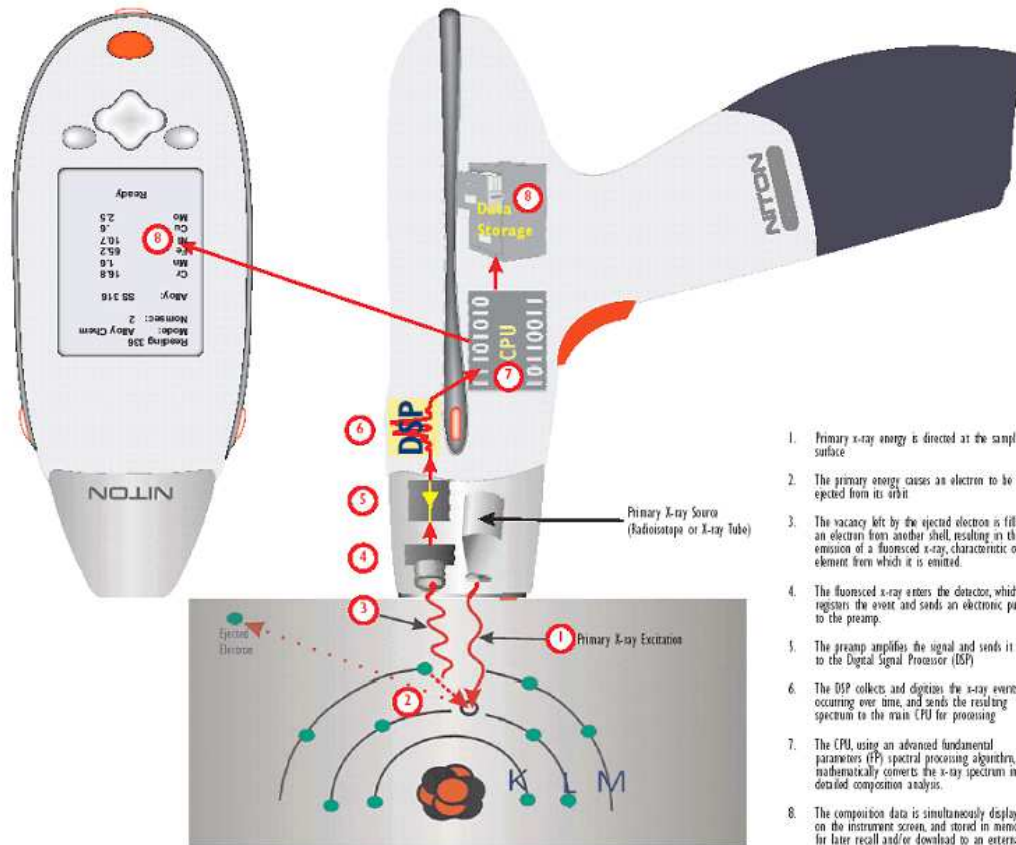


Exposure Assessment

- Airborne PM10 PM2.5 (personal/stationary indoor/outdoor)
- Deposited Dust (indoor/outdoor/attic)
- Soil (surface – 10 cm layers)
- Dietary intake (Mn, Fe, Se, Zn)
- Leafy and root vegetables
- Water (public water supply/private wells)
- Biomarkers (blood, urine, hair, nails, saliva, teeth)



Portable XRFluorescence + GPS reader

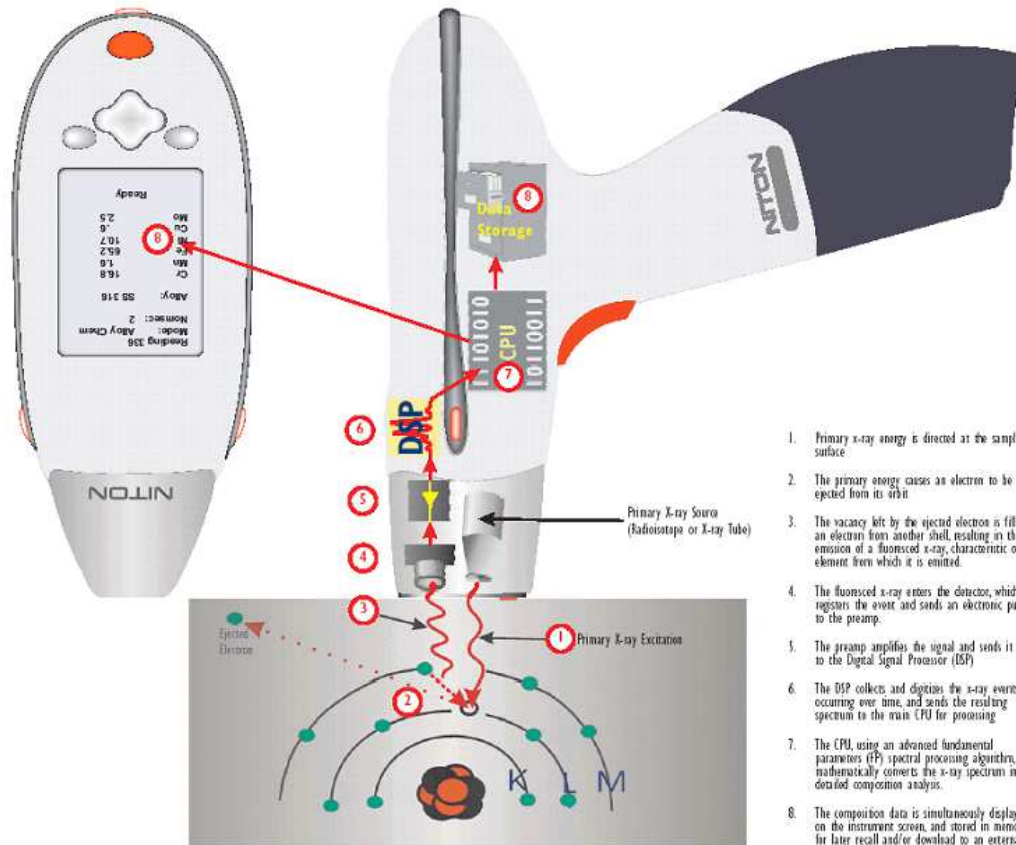


1. Primary x-ray energy is directed at the sample surface
2. The primary energy causes an electron to be ejected from its orbit
3. The vacancy left by the ejected electron is filled by an electron from another shell, resulting in the emission of a fluoresced x-ray, characteristic of the element from which it is emitted.
4. The fluoresced x-ray enters the detector, which registers the event and sends an electronic pulse to the preamp.
5. The preamp amplifies the signal and sends it on to the Digital Signal Processor (DSP)
6. The DSP collects and digitizes the x-ray events occurring over time, and sends the resulting spectrum to the main CPU for processing
7. The CPU, using an advanced fundamental parameters (FP) spectral processing algorithm, mathematically converts the x-ray spectrum into a detailed composition analysis.
8. The composition data is simultaneously displayed on the instrument screen, and stored in memory for later recall and/or download to an external PC



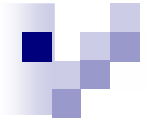


Portable XRFluorescence + GPS reader



1. Primary x-ray energy is directed at the sample surface
2. The primary energy causes an electron to be ejected from its orbit
3. The vacancy left by the ejected electron is filled by an electron from another shell, resulting in the emission of a fluoresced x-ray, characteristic of the element from which it is emitted.
4. The fluoresced x-ray enters the detector, which registers the event and sends an electronic pulse to the preamp.
5. The preamp amplifies the signal and sends it on to the Digital Signal Processor (DSP)
6. The DSP collects and digitizes the x-ray events occurring over time, and sends the resulting spectrum to the main CPU for processing
7. The CPU, using an advanced fundamental parameters (FP) spectral processing algorithm, mathematically converts the x-ray spectrum into a detailed composition analysis.
8. The composition data is simultaneously displayed on the instrument screen, and stored in memory for later recall and/or download to an external PC

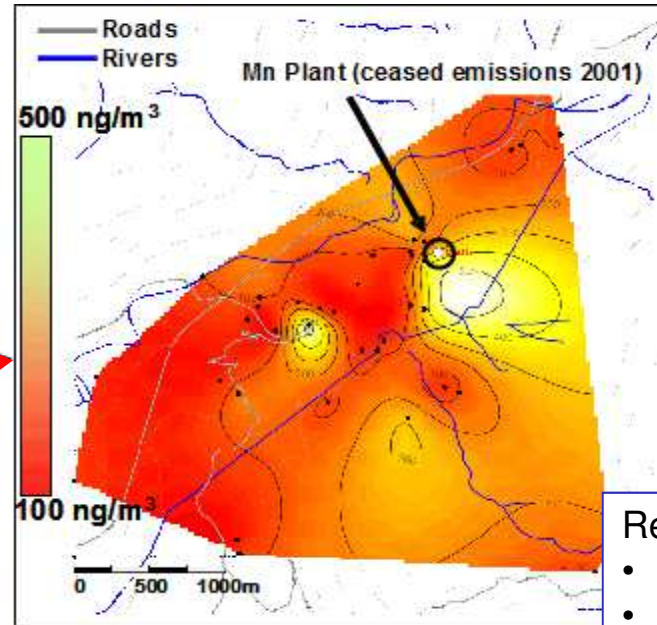
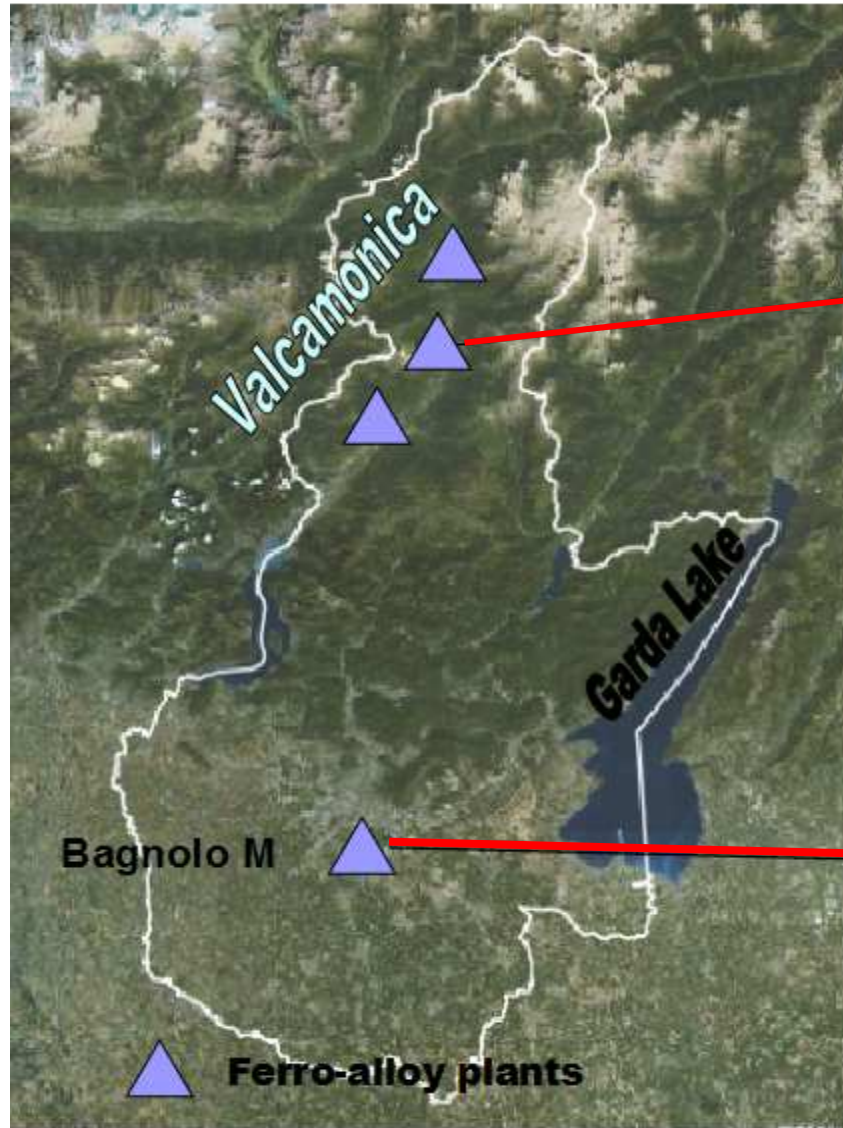




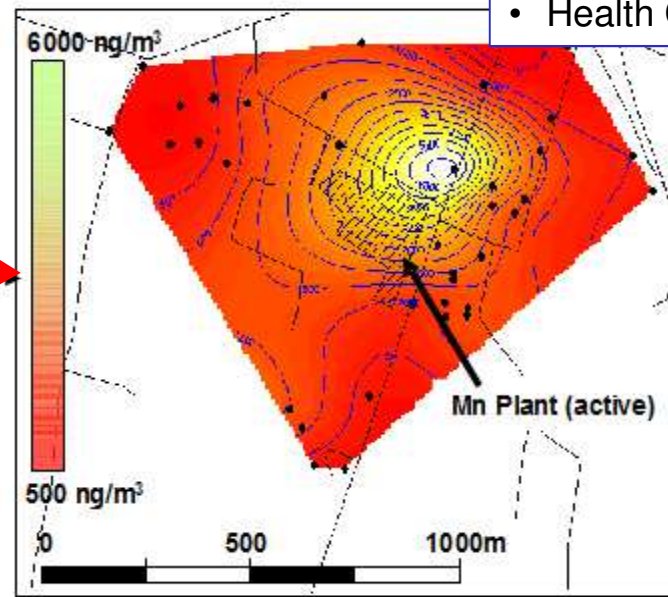
Personal 24h sampling at 10 l/min flow rate (SKC Leland Legacy)



PM10
Personal
Environmental
Monitor



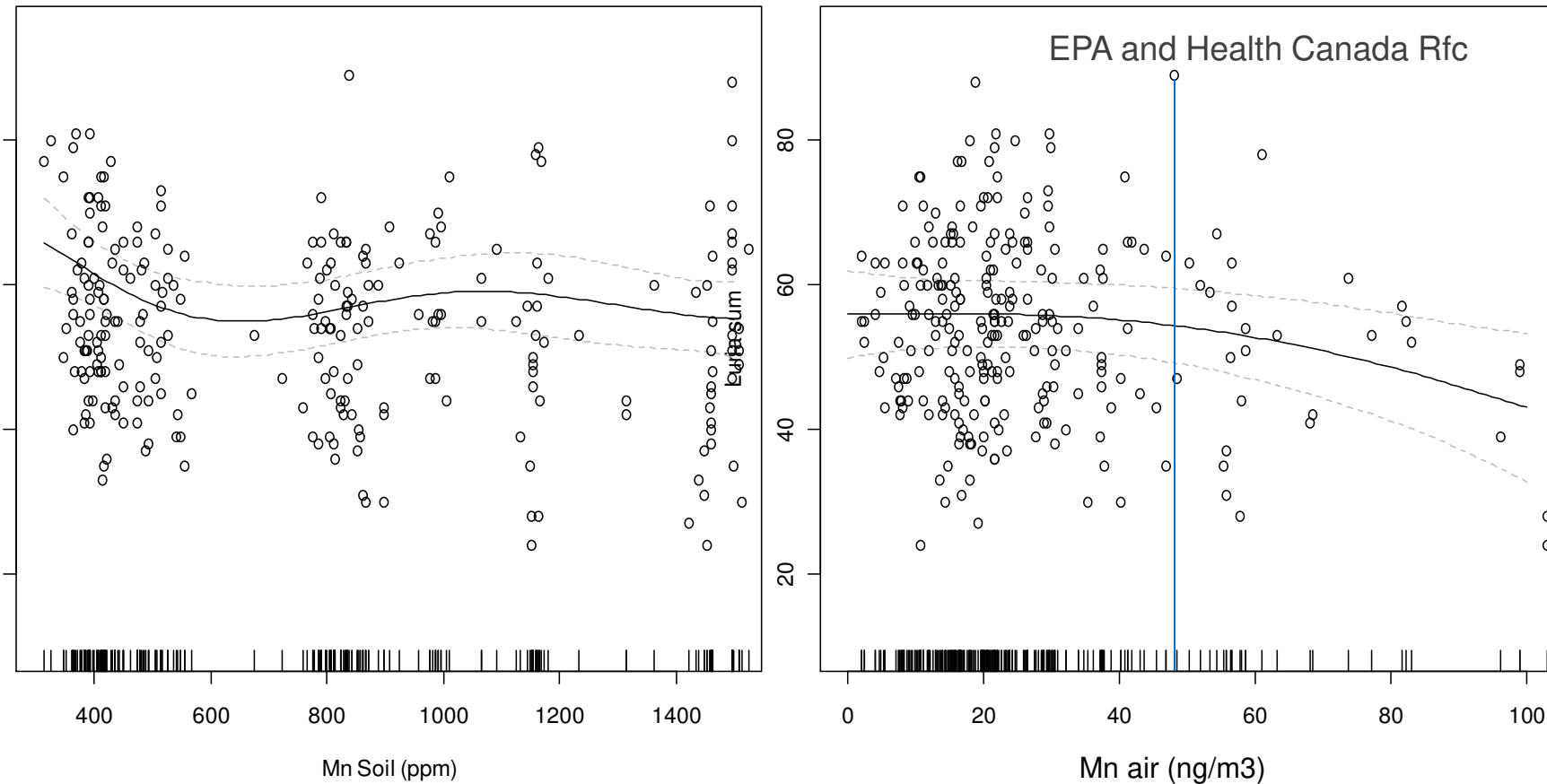
- Ref. Values (ng/m³):
- WHO 100
 - EPA 50
 - Health Canada 50



Elderly



Motor coordination

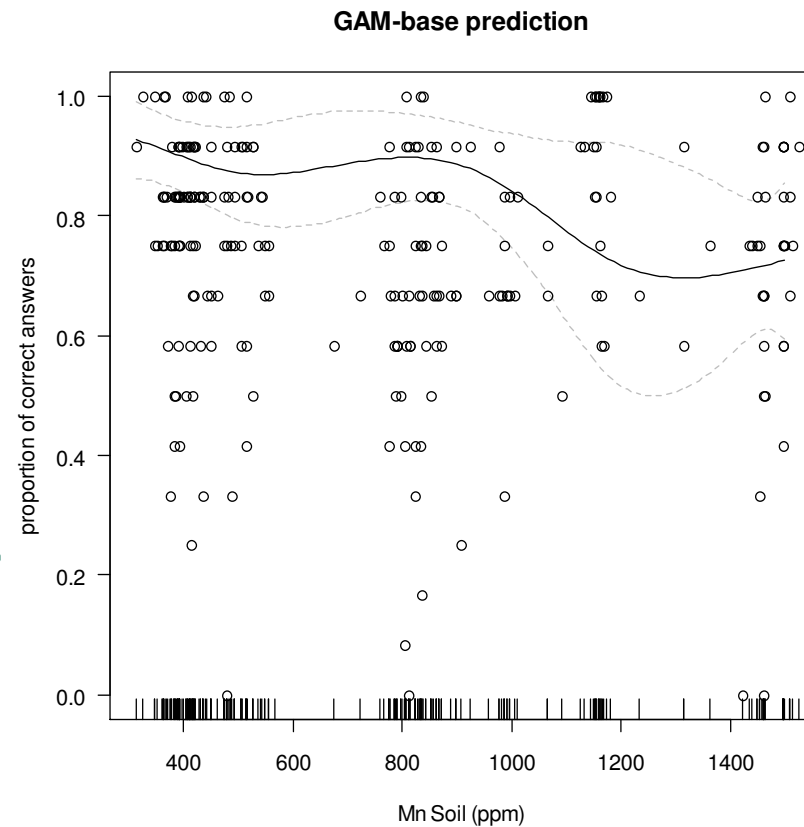


Lucchini RG et al. Neurofunctional Dopaminergic impairment in elderly after lifetime exposure to manganese. *Neurotoxicol* 2014;45:309-17

Olfactory discrimination

<i>Parametric:</i>	<i>Estimate</i>	<i>Std. Error</i>	<i>z value</i>	<i>Pr(> z)</i>
(Intercept)	1.4153	0.1738	8.144	0.0000
Smoke	-0.4189	0.2531	-1.656	0.0978
Gender	-0.1899	0.2132	-0.891	0.3732
Non parametric	edf	Ref.df	Chi.sq	p
s(MnSoil)	3.886	4.734	18.623	0.0018
s(log(PM10))	1.000	1.000	0.589	0.4428
s(log(MnAir))	1.151	1.282	0.228	0.7357
s(age)	4.567	4.897	30.724	0.0000

Adjusted effect of Mn on the olfactory test (semi-parametric GAM logistic model)



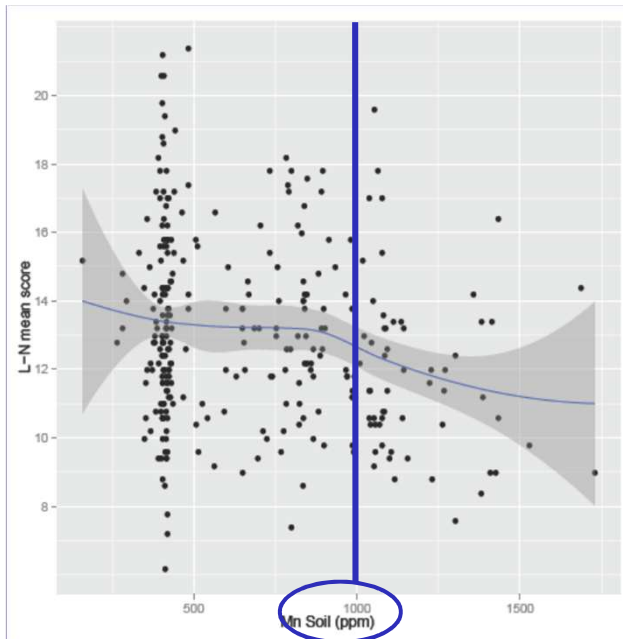
Adolescents



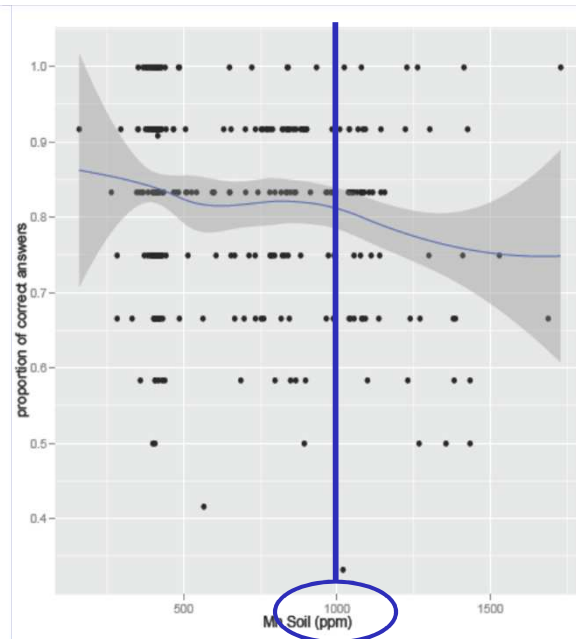


Motor/odor effects in adolescents

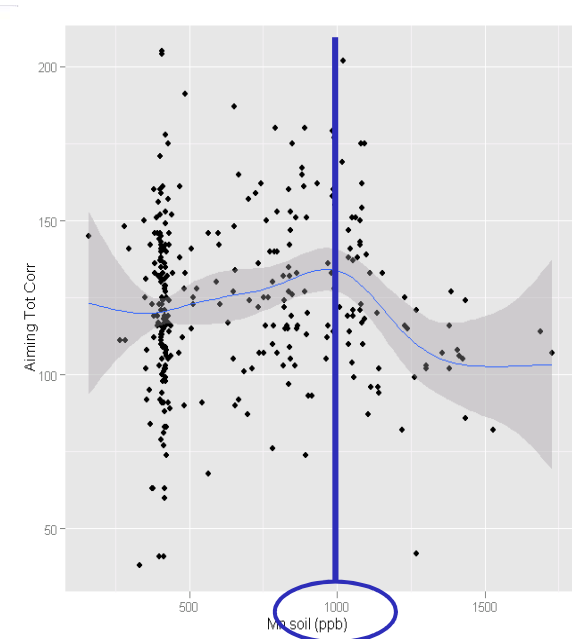
Motor Coordination



Odor Identification



Hand Steadiness

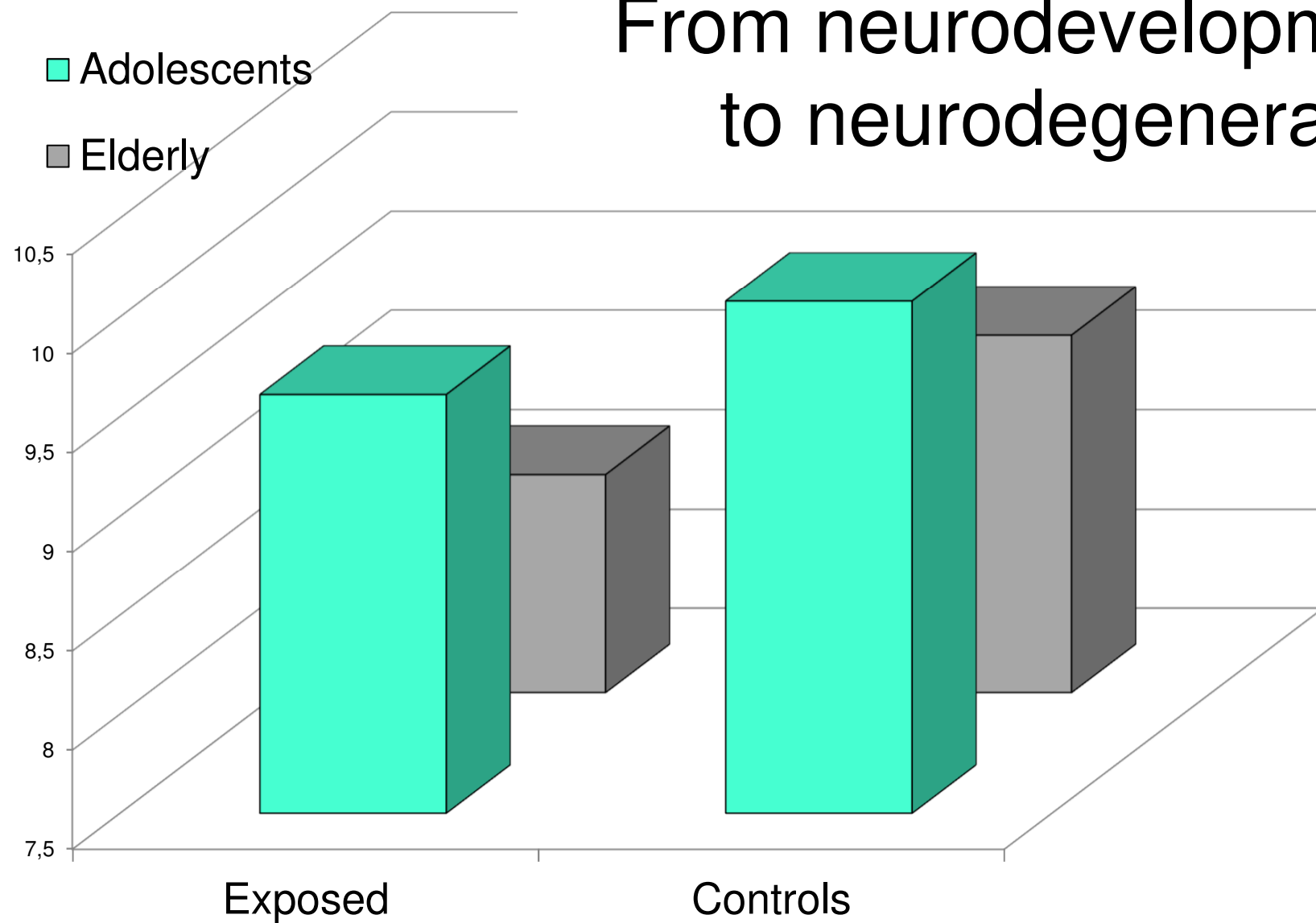


Cut-off soil Mn ~1000 ppm

Lucchini et al. Tremor, olfactory and motor changes in Italian adolescents exposed to historical ferro-manganese emission. *Neurotoxicology*. 2012 Aug;33(4):687-96



From neurodevelopment to neurodegeneration



Zoni et al. Olfactory functions at the intersection between environmental exposure to manganese and Parkinsonism. *J Trace Elem Med Biol.* 2012;26(2-3):179-82.

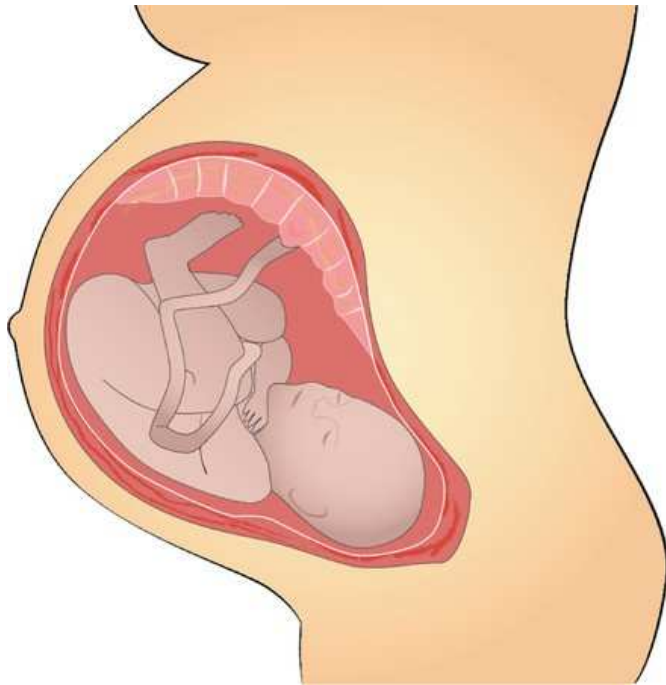
Teeth Biomarkers



Environment health and critical windows



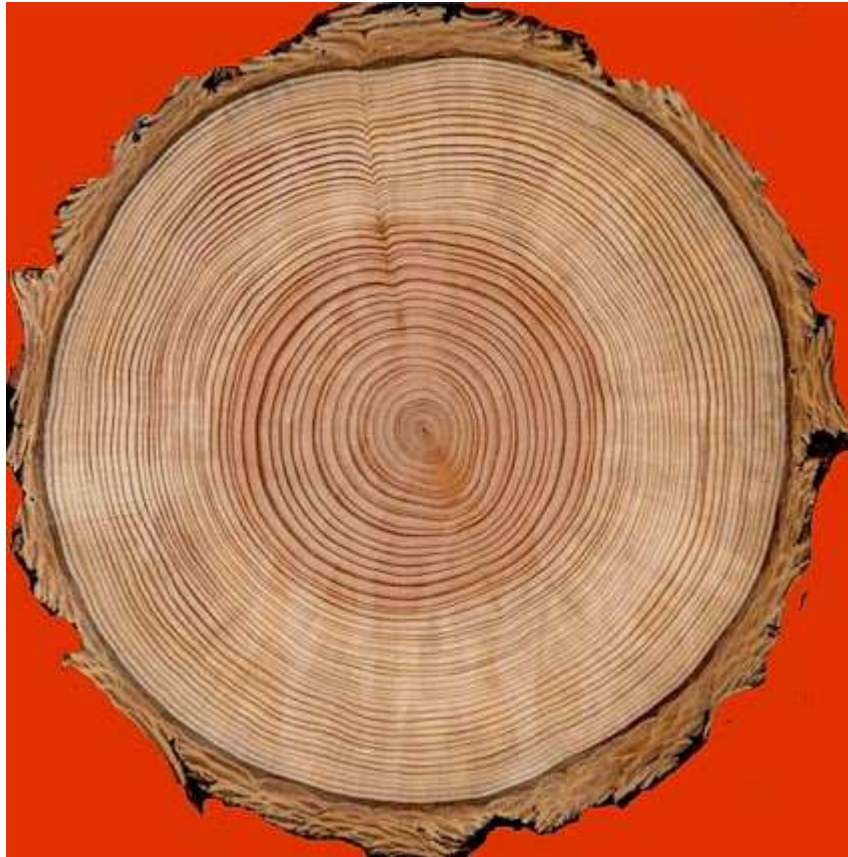
Challenges to estimating prenatal exposure

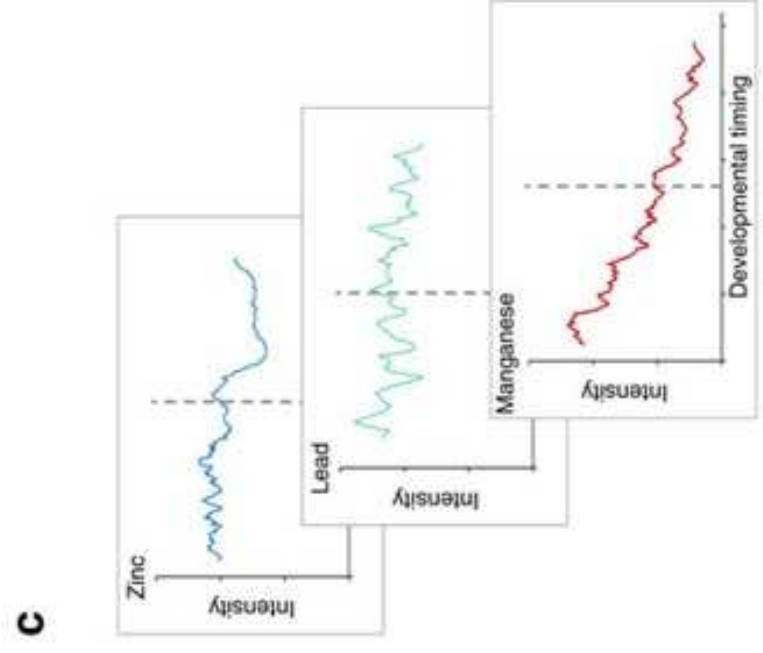
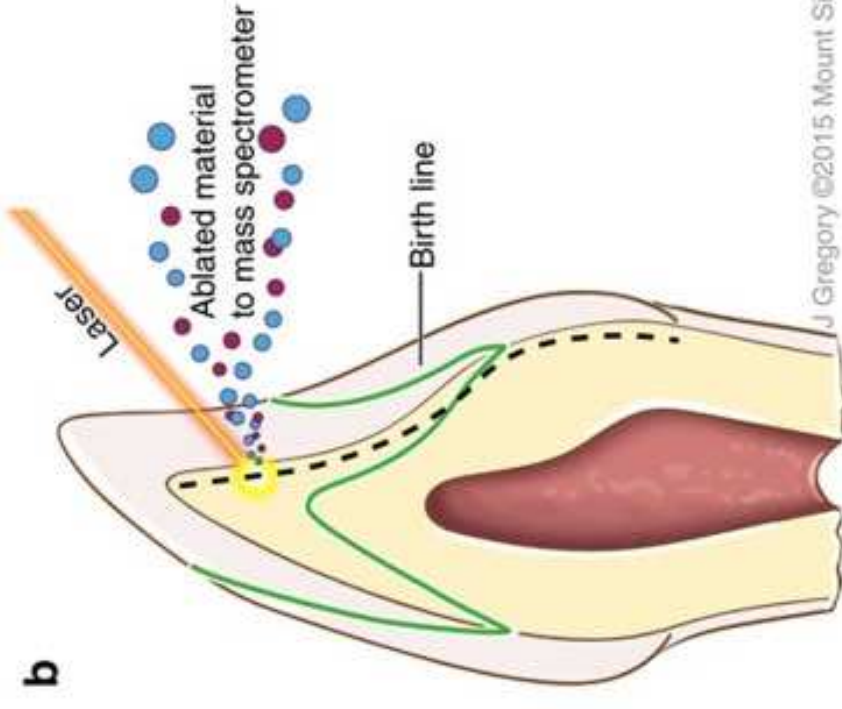
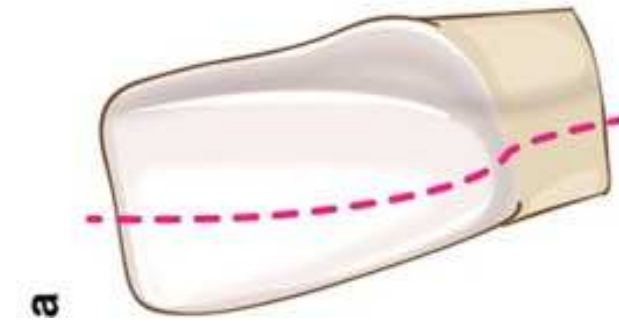


- Variable partitioning across placenta
- Maternal biomarkers may not reflect fetal exposure
- Not feasible to obtain fetal tissue during pregnancy



Exposure timing....retrospectively?!





J Gregory ©2015 Mount Sinai Health System

[Find a Doctor](#)[Request an Appointment](#)[Our Locations](#)[Patient Care](#)**Manish Arora, PhD** **Positions:** ASSOCIATE PROFESSOR | Environmental Medicine & Public Health,
ASSOCIATE PROFESSOR | Dentistry**National Institutes of Health**
Turning Discovery Into Health[Health Information](#)[Grants & Funding](#)[News & Events](#)[Research & Training](#)[Home](#) » [News & Events](#) » [News Releases](#)

NEWS RELEASES

Thursday, June 1, 2017

Baby teeth link autism and heavy metals, NIH study suggests

**Arora et al., Fetal and postnatal metal dysregulation in autism.
Nature Communications. 2017; 8: 15493.**



Contents lists available at ScienceDirect

Environmental Research

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



Sex differences in sensitivity to prenatal and early childhood manganese exposure on neuromotor function in adolescents

Environment International 108 (2017) 299–308




Contents lists available at ScienceDirect

Environment International

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



Manganese in teeth and neurobehavior: Sex-specific windows of susceptibility

Julia Anglen Bauer^{a,*}, Birgit Claus He
Giuseppa Cagna^c, Donatella Placidi^c, J
Donald Smith^f, Roberto G. Lucchini^{b,c}

G. Maekel
NEUTOX 2241 No. of Pages 7

ARTICLE IN PRESS

NeuroToxicology xxx (2017) xxx–xxx



Contents lists available at ScienceDirect

NeuroToxicology



Full Length Article

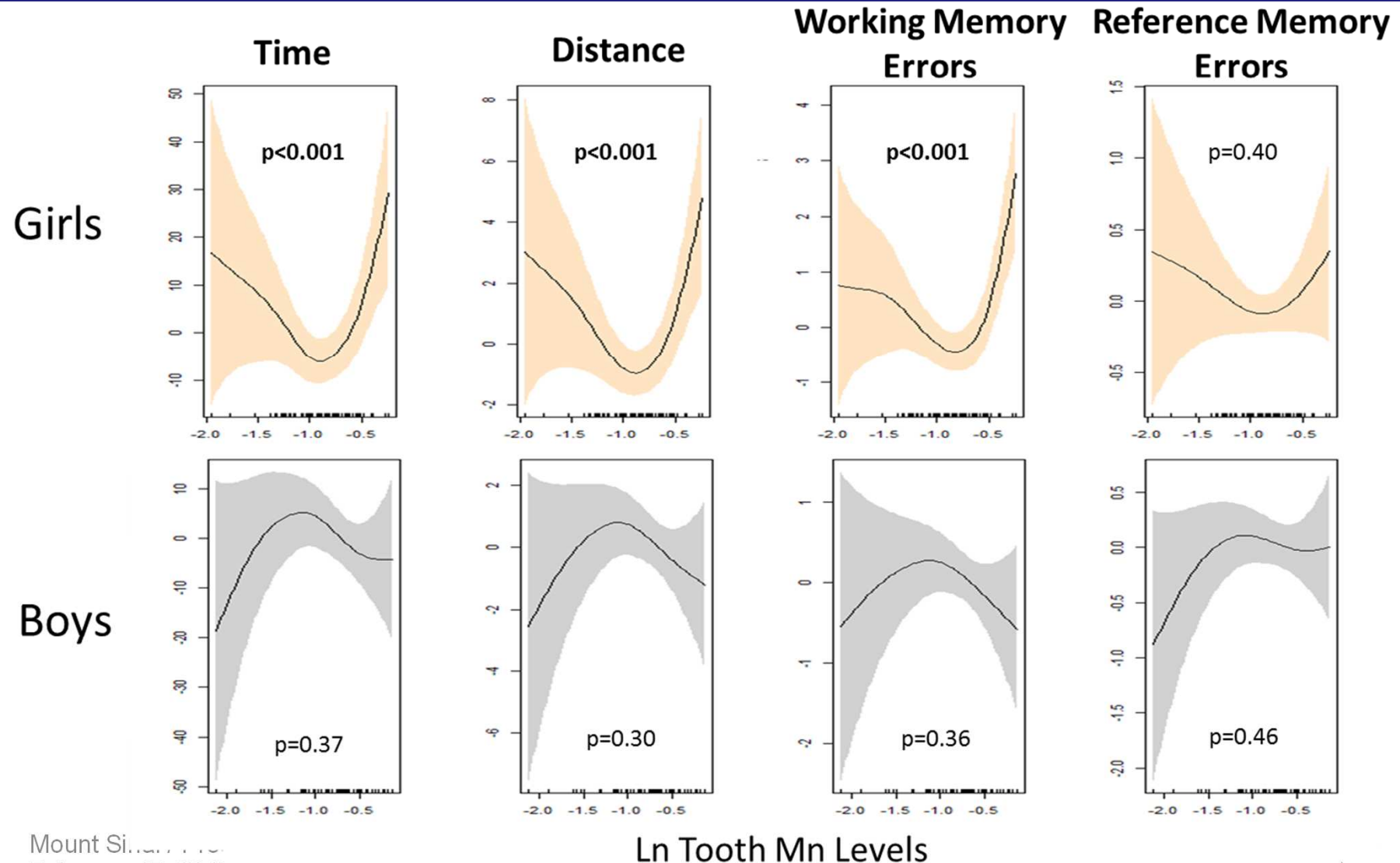
Polymorphisms in manganese transporters show developmental stage and sex specific associations with manganese concentrations in primary teeth

Virtual Radial Arm Maze (VRAM)

- Computerized test with joystick
- Objective: find reward in 4 of 8 arms, across 8 trials
- Four performance measures per trial:
 - Time/Latency
 - Distance traveled
 - Working memory errors
 - Reference memory errors
- *Lower scores = better performance*



Prenatal Mn & VRAM: Sex-specific associations





Summary

- ▶ ↑ prenatal Mn: better motor function in boys
 - body stability (Sway test)
 - hand/finger coordination (LURIA test)
 - eye-hand coordination (Pursuit Aiming)
- ▶ ↑ prenatal Mn: worse body stability in girls
- ▶ ↑ prenatal Mn: ↑ tremor frequency in girls;
↑ childhood Mn: ↑ tremor frequency in boys
- ▶ These data potentially support the sex-specific associations and existence of critical windows depending on the measured domains



Newsweek

TECH & SCIENCE


9/11 CHILDREN: SCIENTISTS FIND TOXINS IN THEIR BABY TEETH

BY **LEAH MCGRATH GOODMAN** ON 9/11/17 AT 11:26 AM

9/11 First Responders: The Continuing Fallout

Newsweek





Mount Sinai, NYC, USA

Roberto Lucchini, Robert Wright,
Manish Arora, Megan Horton,
Cheuk Tang, Maria Rosa,
Mathilda Chiu, Leon Hsu

UC Santa Cruz USA

Donald Smith, Stephan Beaudin,
Tom Jursa

Columbia University

Benjamin Bostick

Karolinska Institute, SWEDEN

Karin Broberg, Karin Wahlberg,
Marie Vahter

University of Brescia, ITALY

Chiara Fedrighi, Giuseppa Cagna, Silvia
Zoni, Stefano Guazzetti, Margherita
Caci, Manuela Oppini, Marco Peli, Laura
Borgese, Roberto Ranzi, Stefano
Barontini, Roberto Gasparotti, Lorella
Mascaro, Claudia Ambrosi, Tiziana
Marinero, Miriana Montemurro

Boston University, USA

Birgit Clauss Henn

Harvard School of Public Health

Brent Coull

ASL Taranto

Michele Conversano, Augusto Giorgino

**FUNDS: EU FOODCT-2006-016253, NIEHS R01ES019222-01, NIEHS
R01ES019222-06, NIEHS P30ES023515, UNIBSCLE 9015, CCM2013,
INAIL60002.02/07/2012, REGLOMBARDIA170174SAL-68**