

Impatto dei metalli sul sistema nervoso a Brescia: dal neurosviluppo alla patologie neurodegenerative

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Outline

1. Studi sui lavoratori
2. Parkinsonismo in provincia di Brescia
3. Adolescenti e anziani
4. Predisposizione genetica
5. Prossimi sviluppi

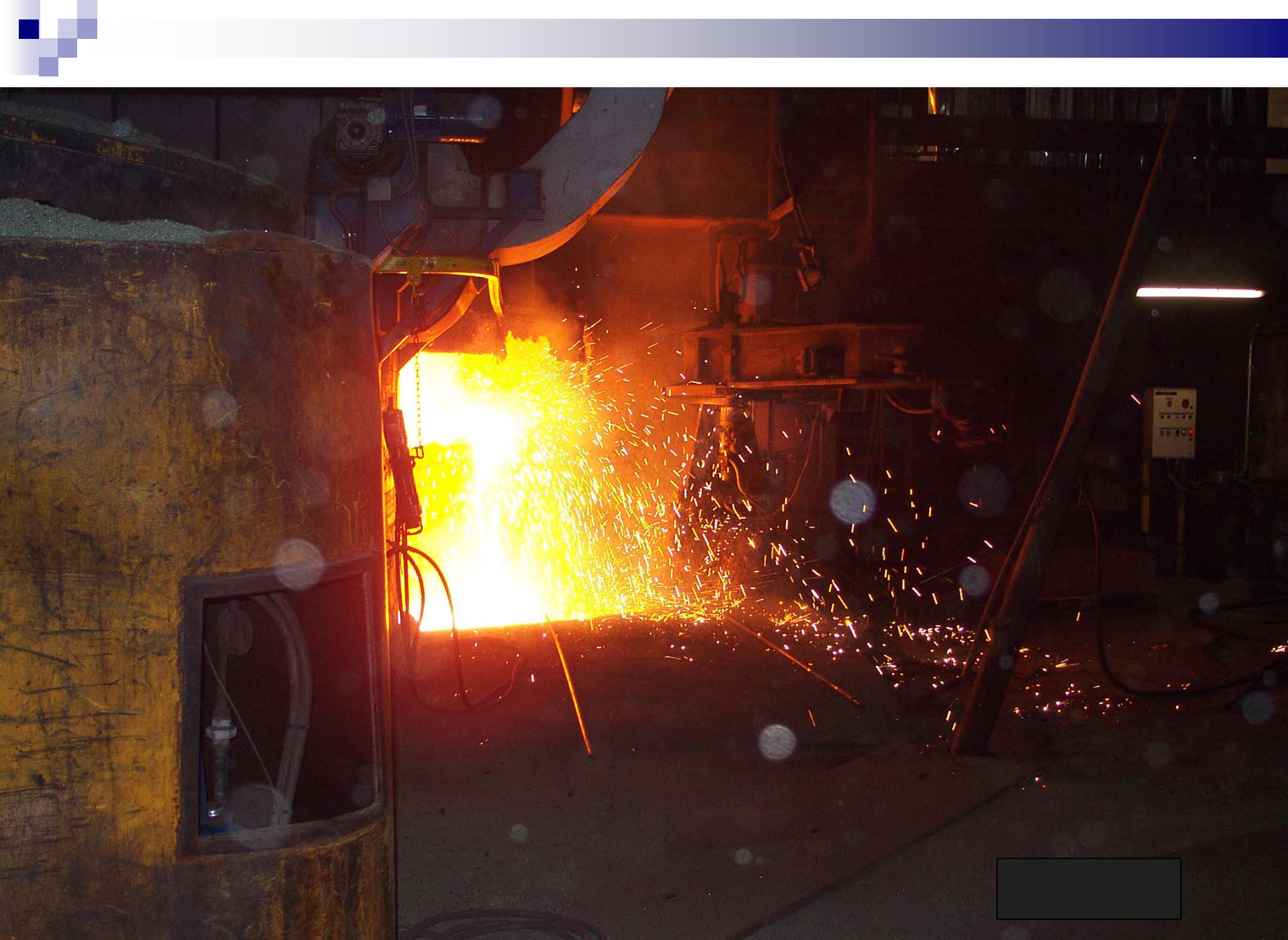
Occupational studies





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

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



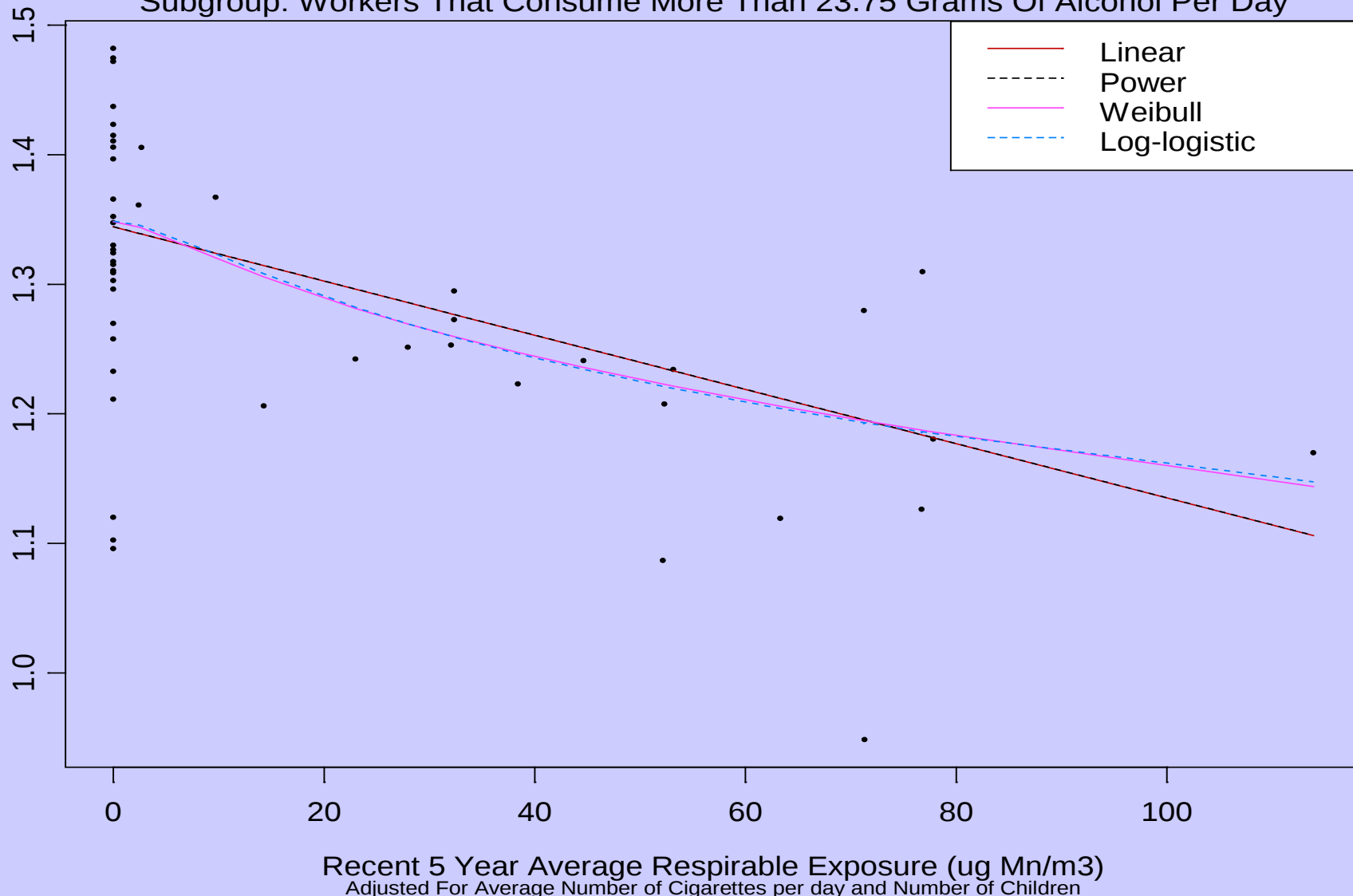


Luria Nebraska Motor Battery



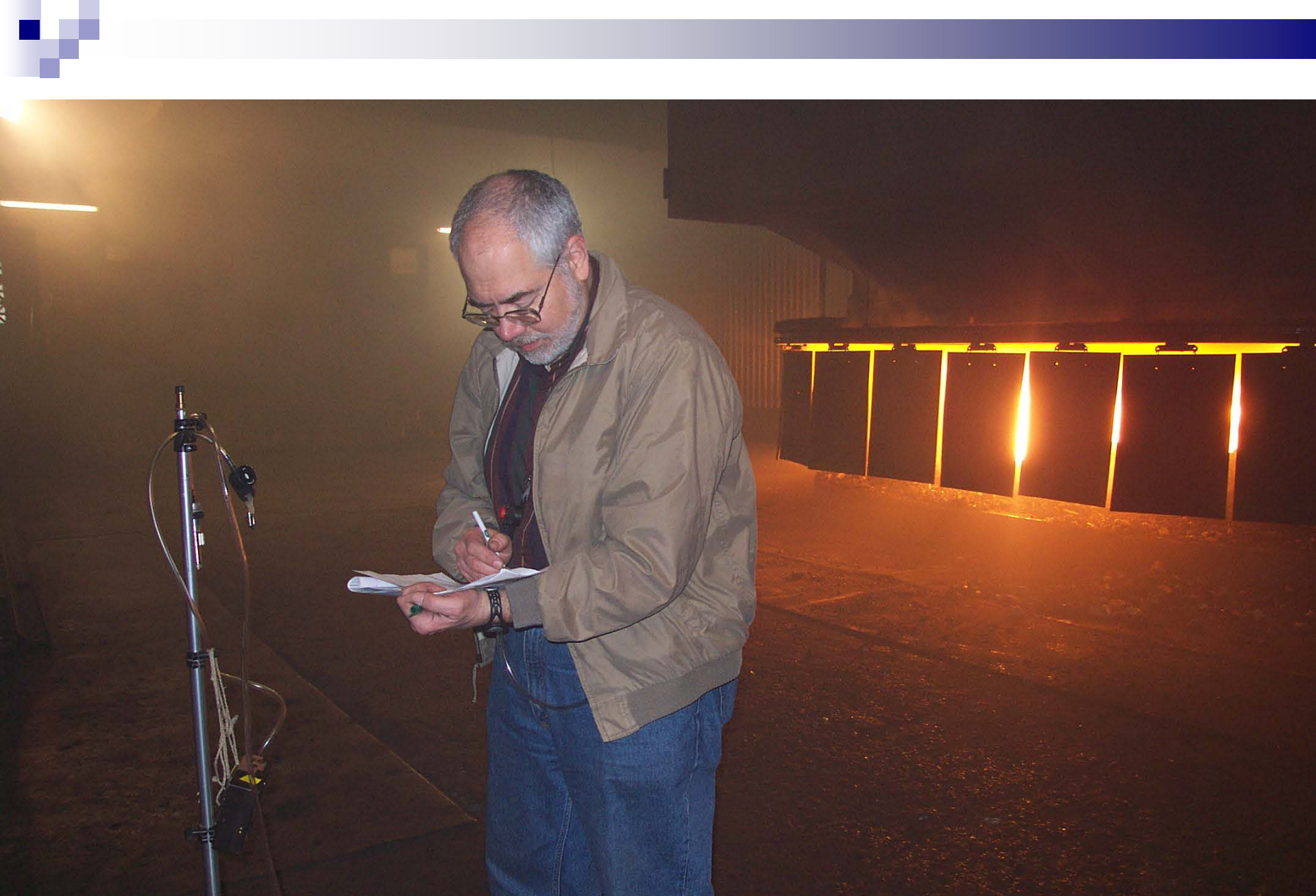
Logarithm Base 10 Transform: LURIA - Thumb and Fingers Non-dominant

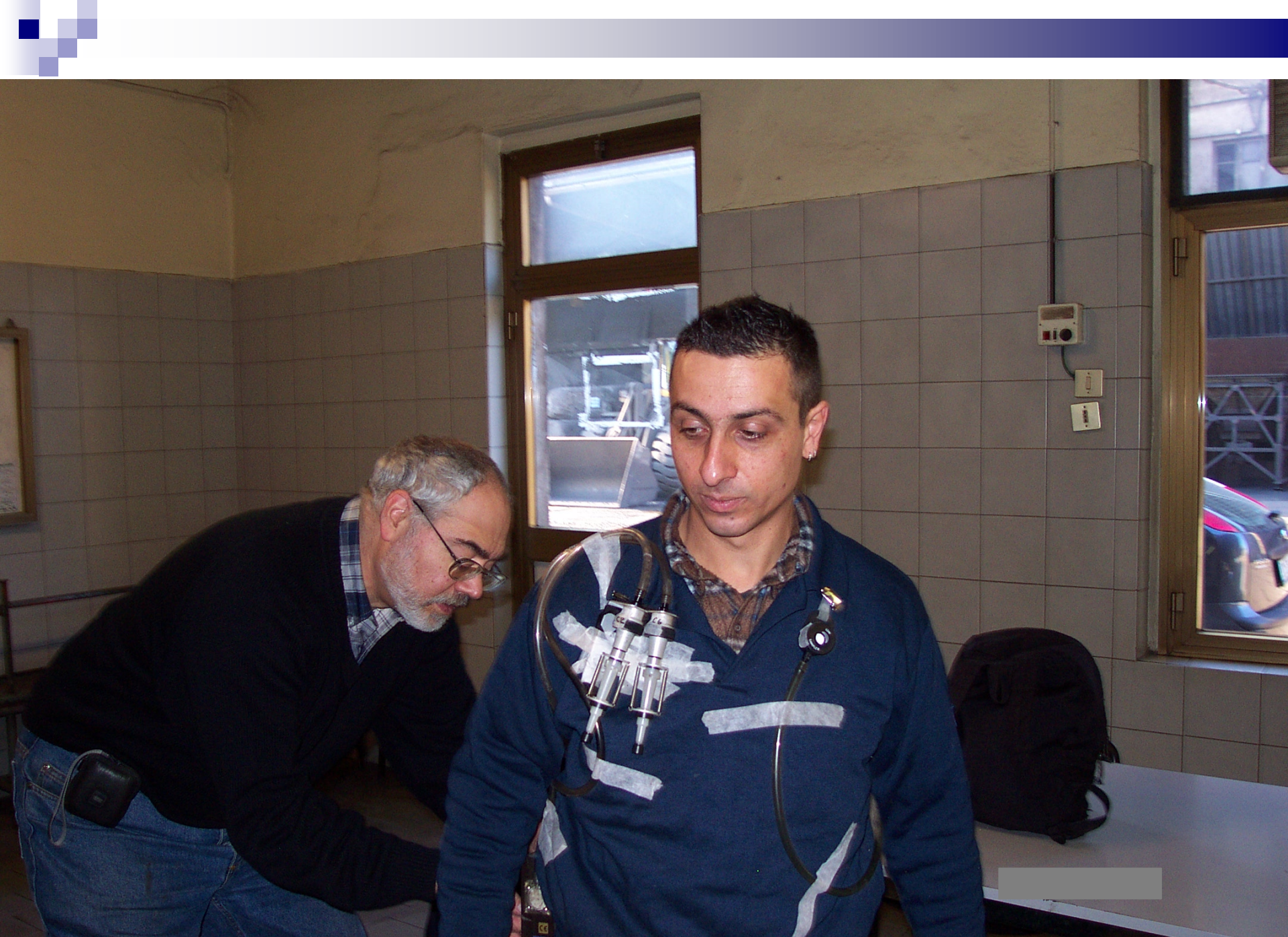
Figure 23: Dose Response Relationship between LURIA Thumb and Fingers and Exposure
Subgroup: Workers That Consume More Than 23.75 Grams Of Alcohol Per Day



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

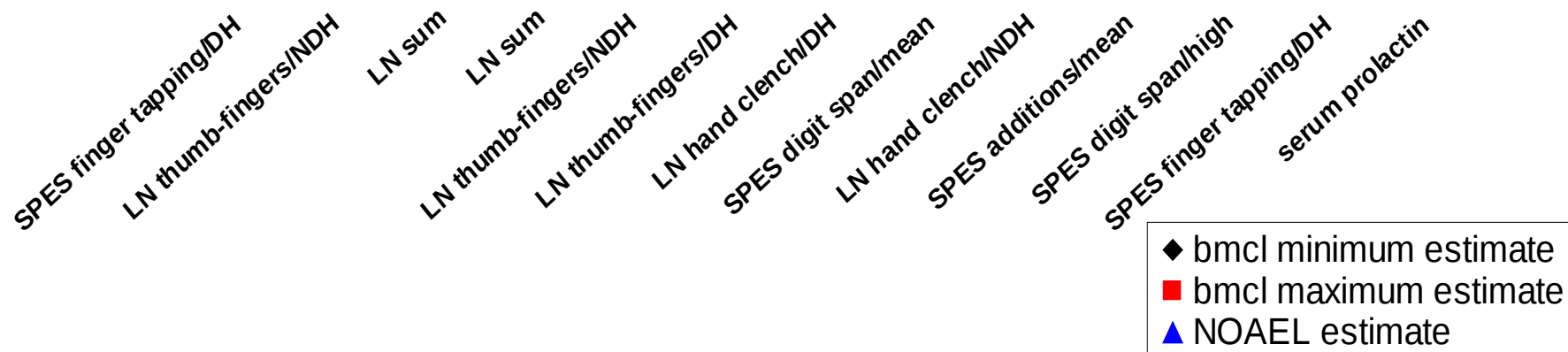
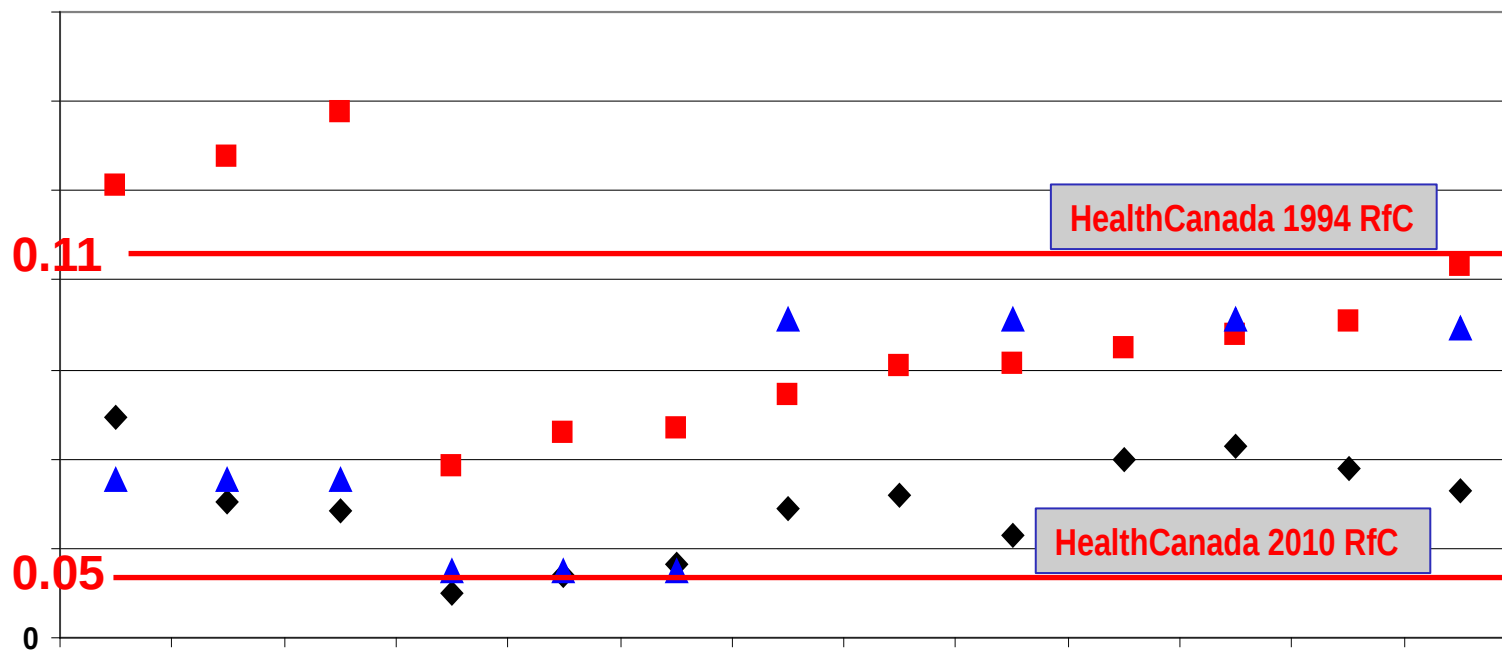






BMCL₀₅'s & NOAELs

bmcl₀₅ or NOAEL (ug/m3)





Neurotoxicology ® 20(2-3), 2897-298, 1999

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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





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
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[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

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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,**

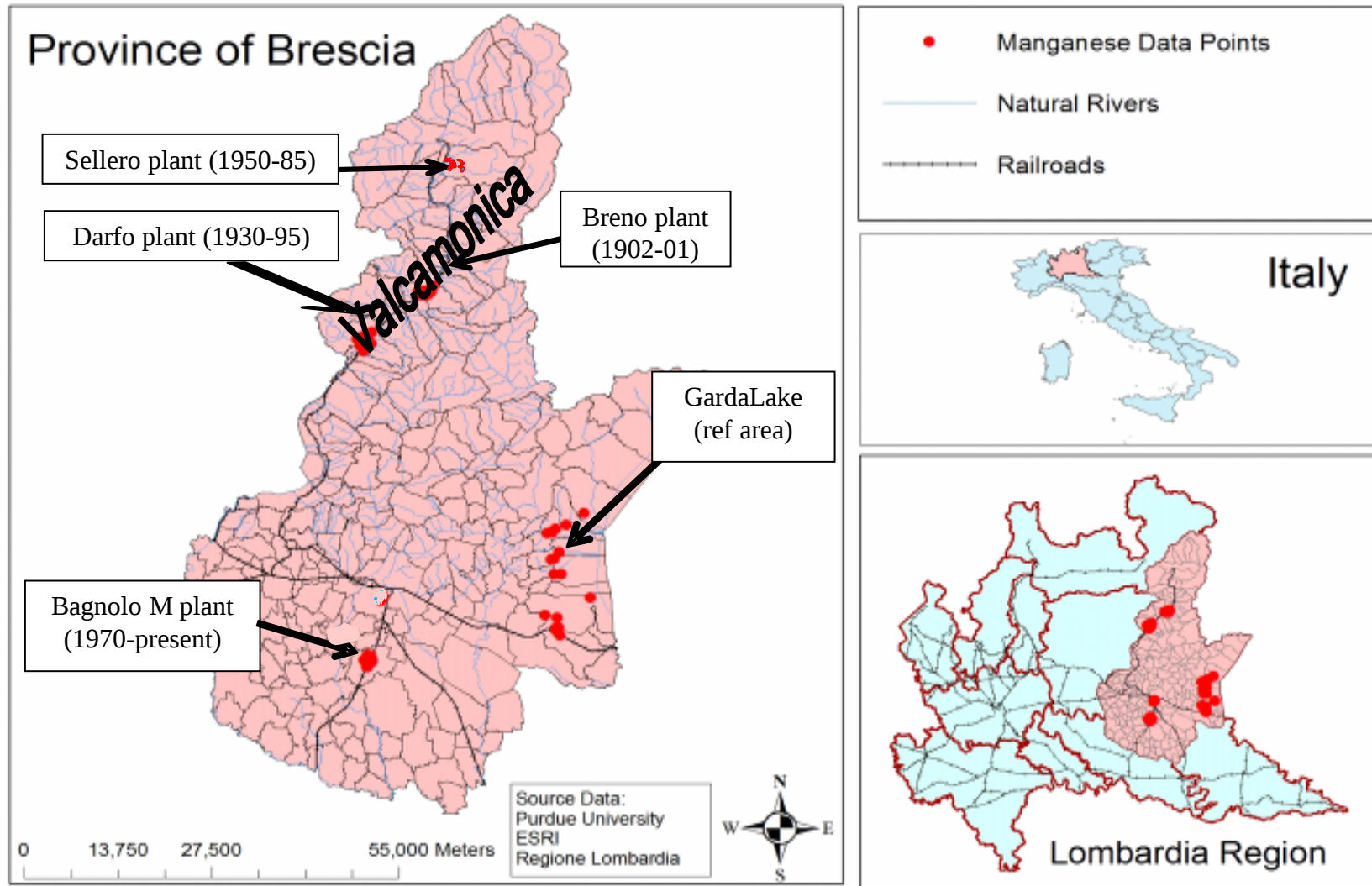
Prevalence of Parkinsonism





23 12 200

Mn exposure from ferroalloy emission

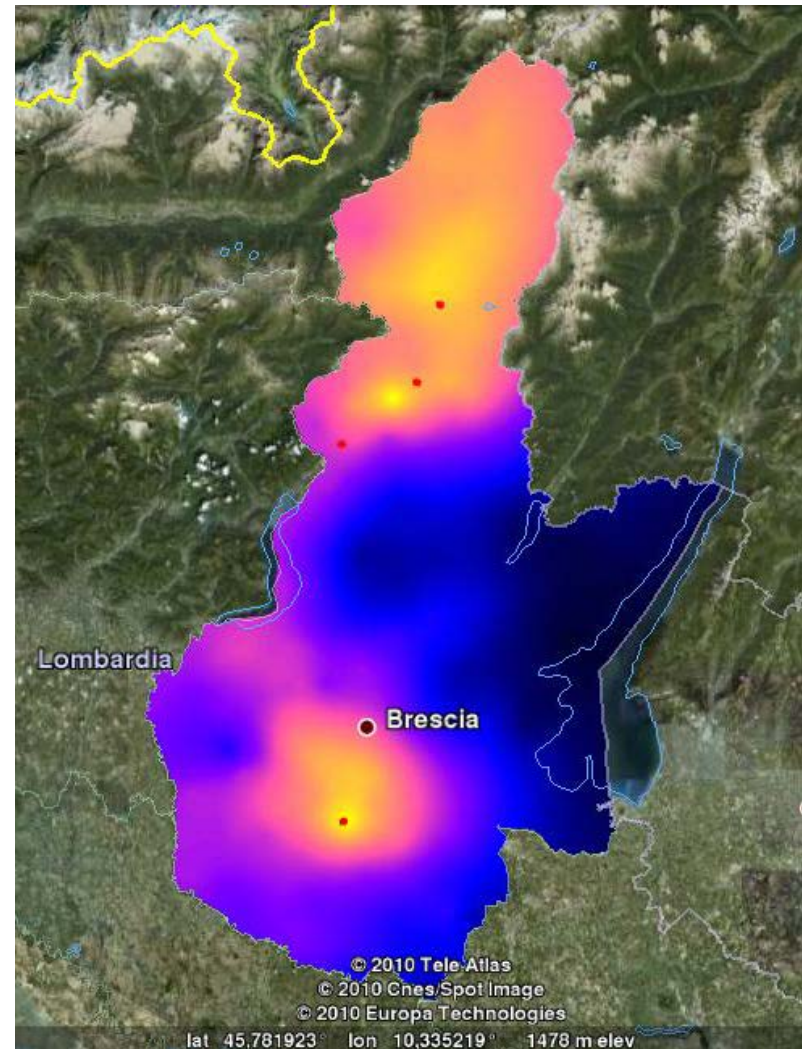
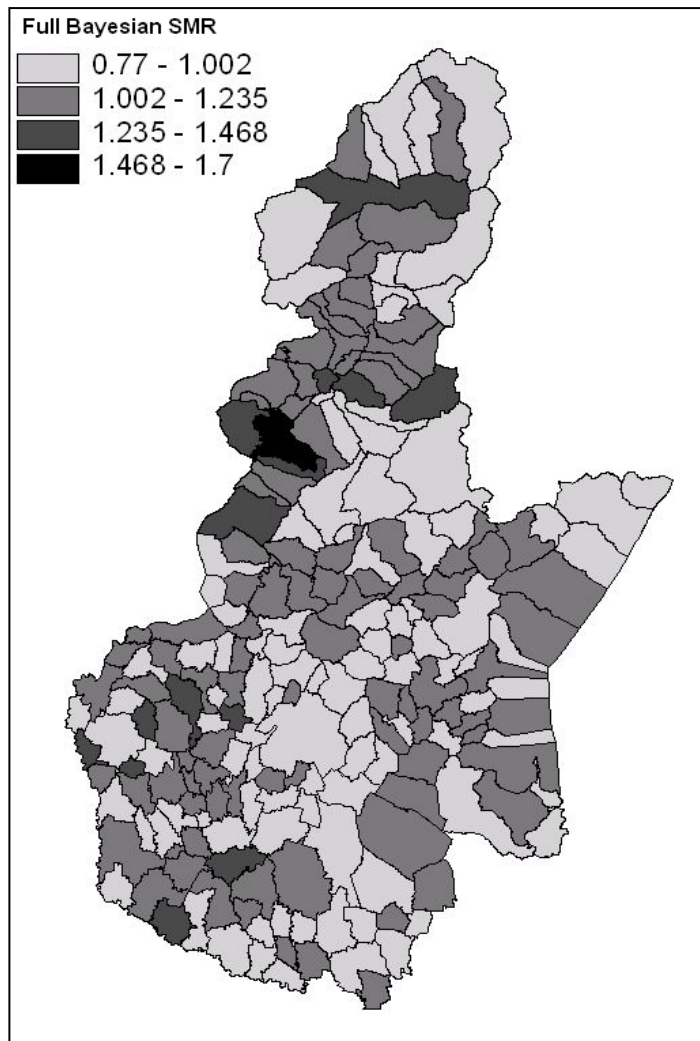


Study site	Cases	Population	Stand prev	Bayesian SMR
Valcamonica	324	77,708	492	1.25
Rest of the Province	2,353	826,289	321	1.00
Total Province	2,677	903,997	407	
Average ITA-EU			150	
SMR = 1.58; CI=1.41-1.76				

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

$p=0.005$



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)

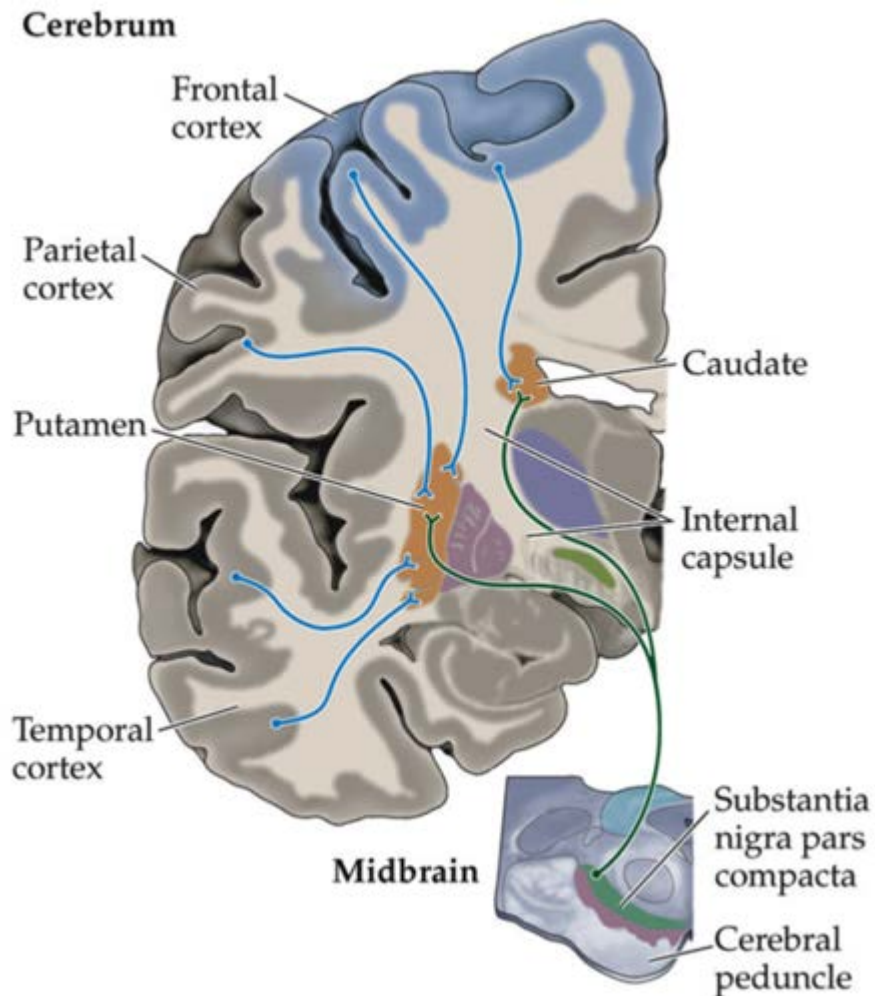


Parkinson's Disease

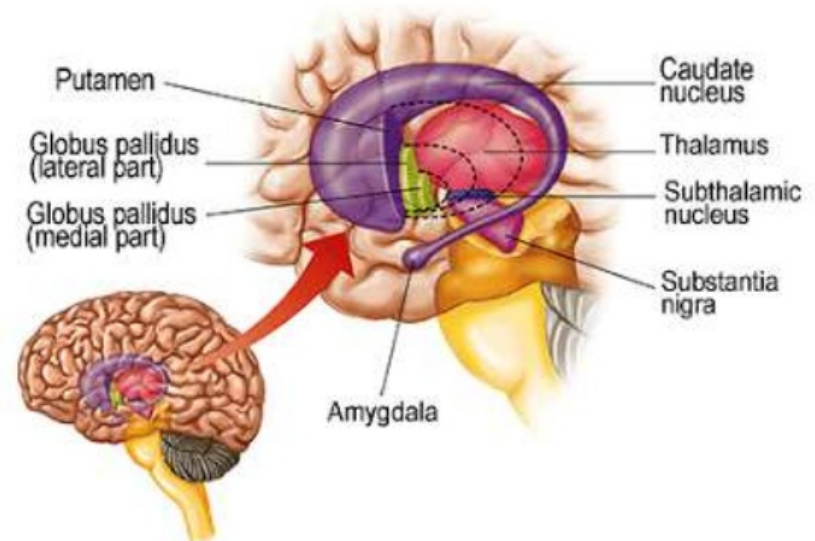
Pathological hallmarks:

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

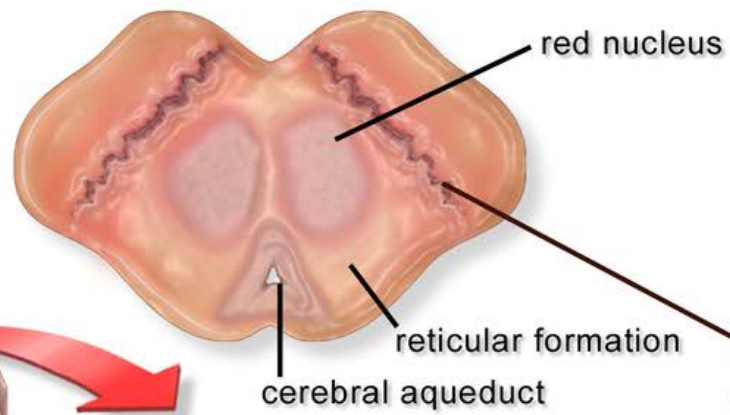
Motor control



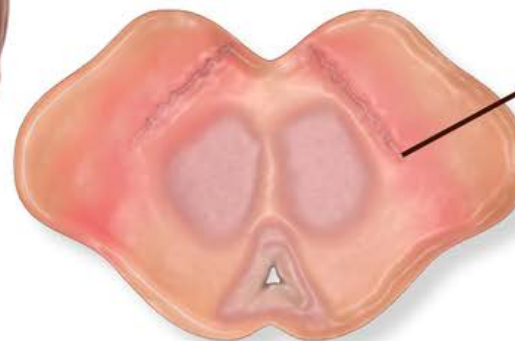
The Human Basal Ganglia



Non-Parkinson's

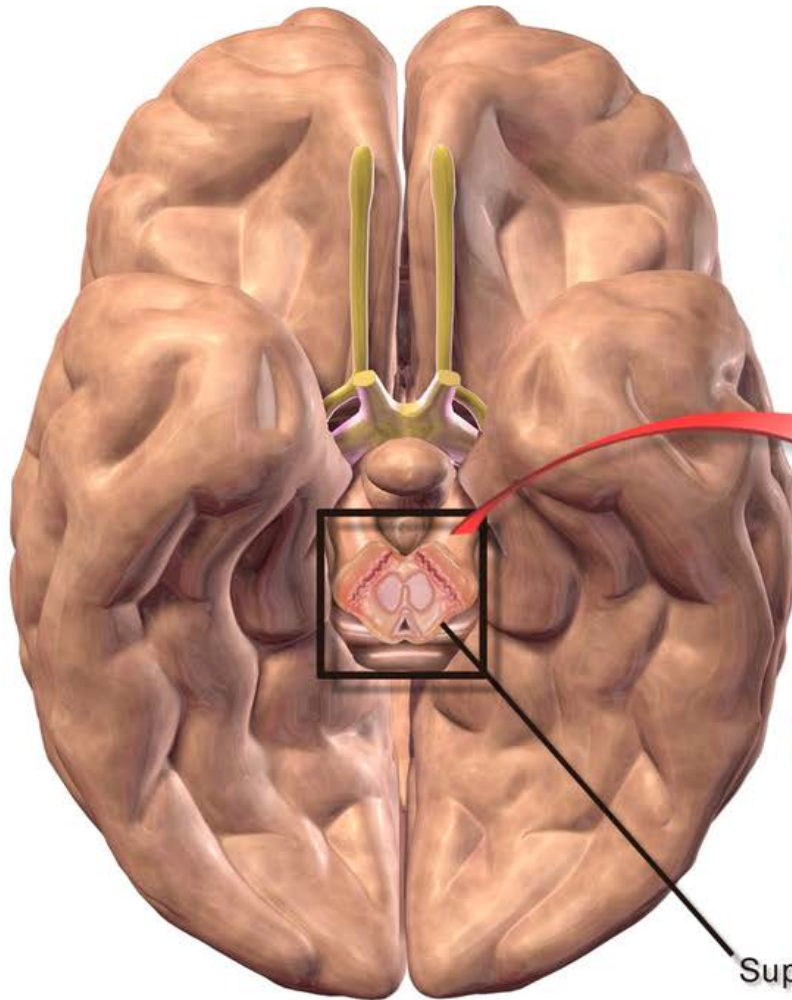


Parkinson's

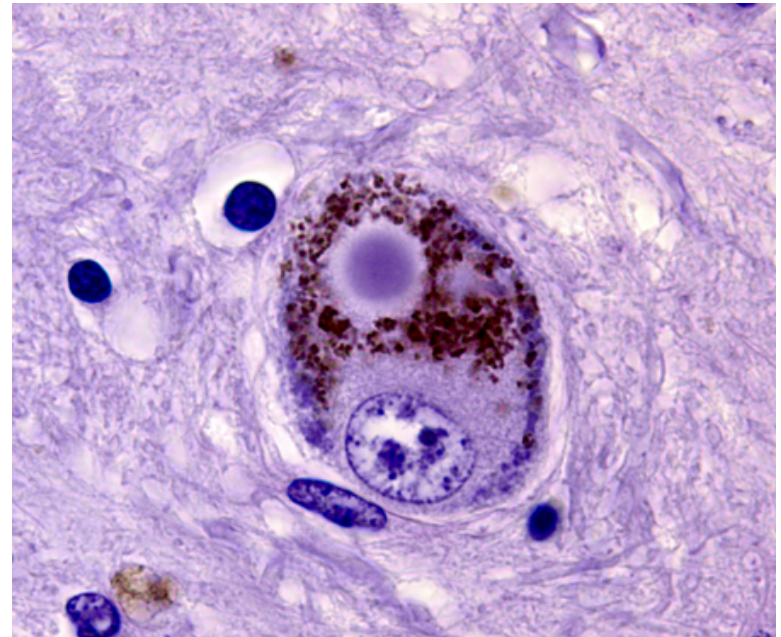


Substantia Nigra

Superior colliculus



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



Monomeric
 α -synuclein



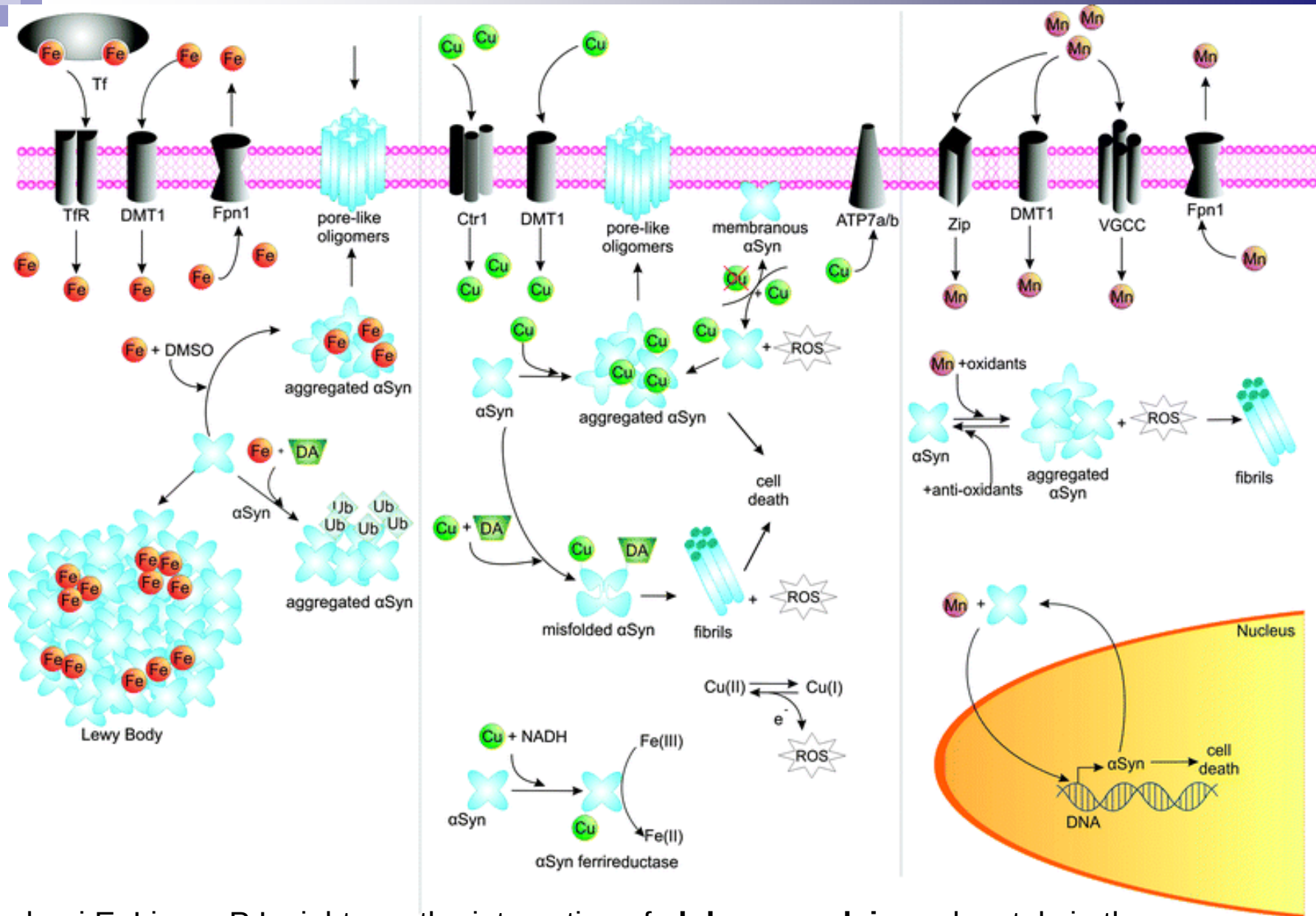
Aggregated
 α -synuclein



α -synuclein
fibrils



Lewy bodies

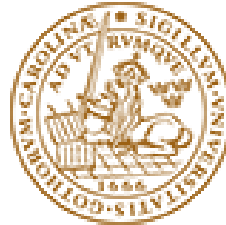


Carboni E, Lingor P Insights on the interaction of **alpha-synuclein** and metals in the pathophysiology of Parkinson's disease. *Metallomics*. 2015 Mar;7(3):395-404.

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

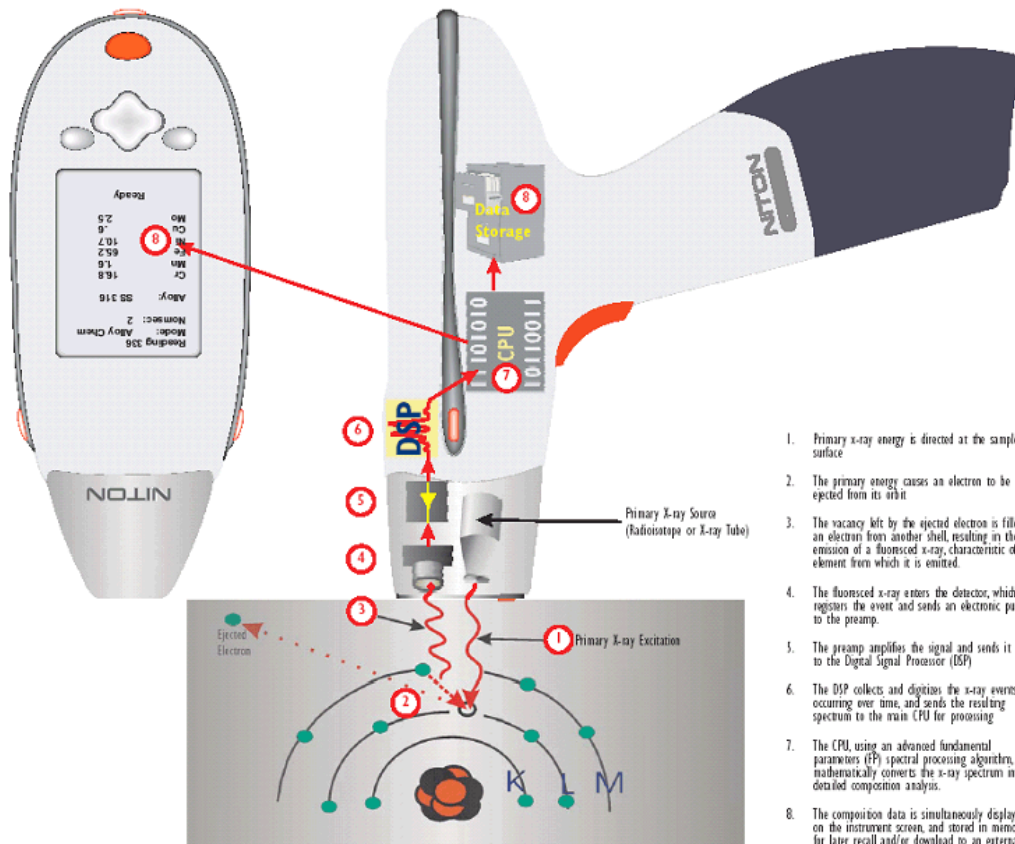




Exposure Assessment

- 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)

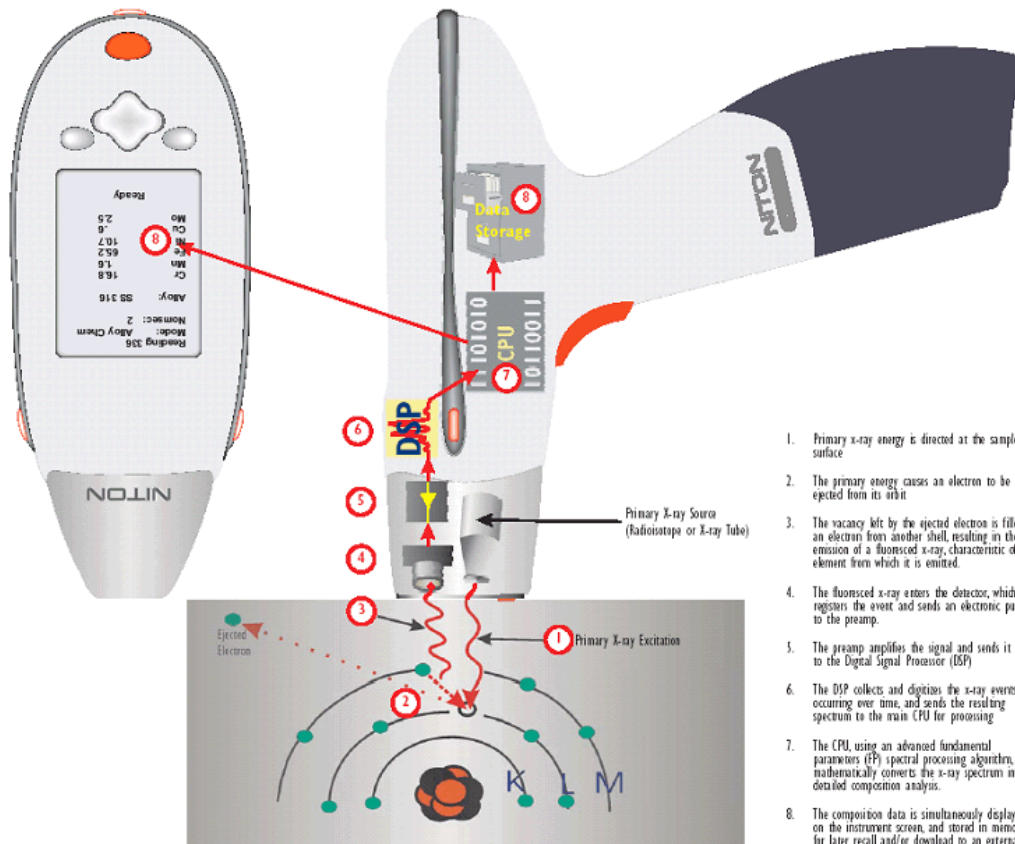
Portable XRFluorescence + GPS reader



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 fluorescent x-ray, characteristic of the element from which it is emitted.
4. The fluorescent 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



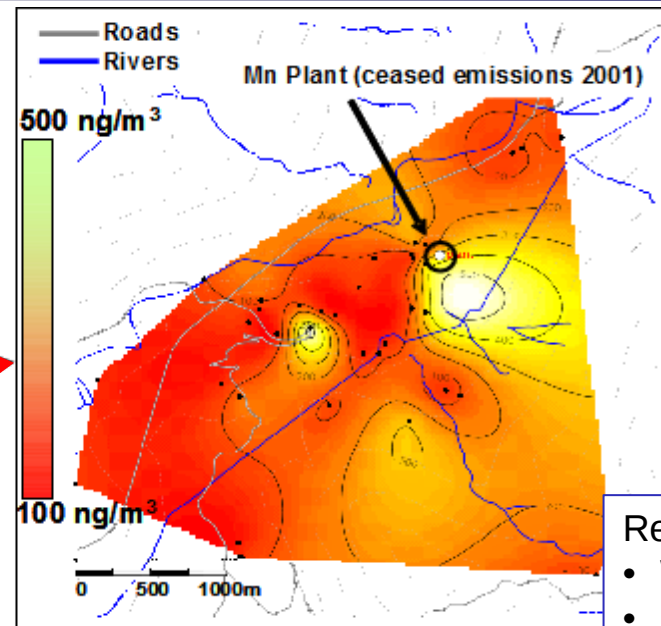
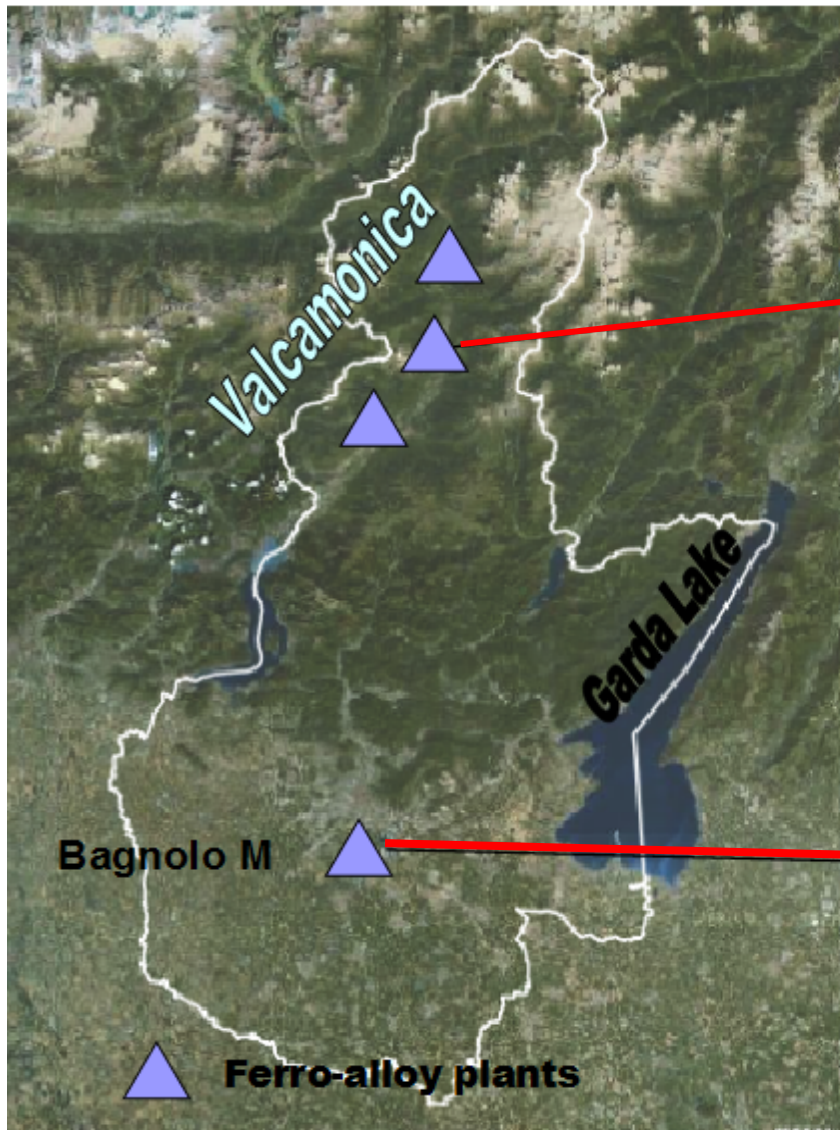
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Personal 24h sampling at 10 l/min flow rate (SKC Leland Legacy)

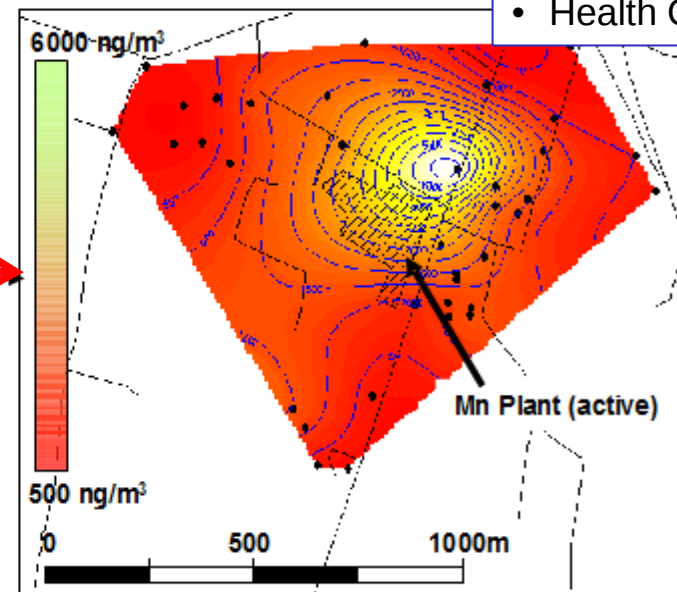


PM10
Personal
Environmental
Monitor



Ref. Values (ng/m³):

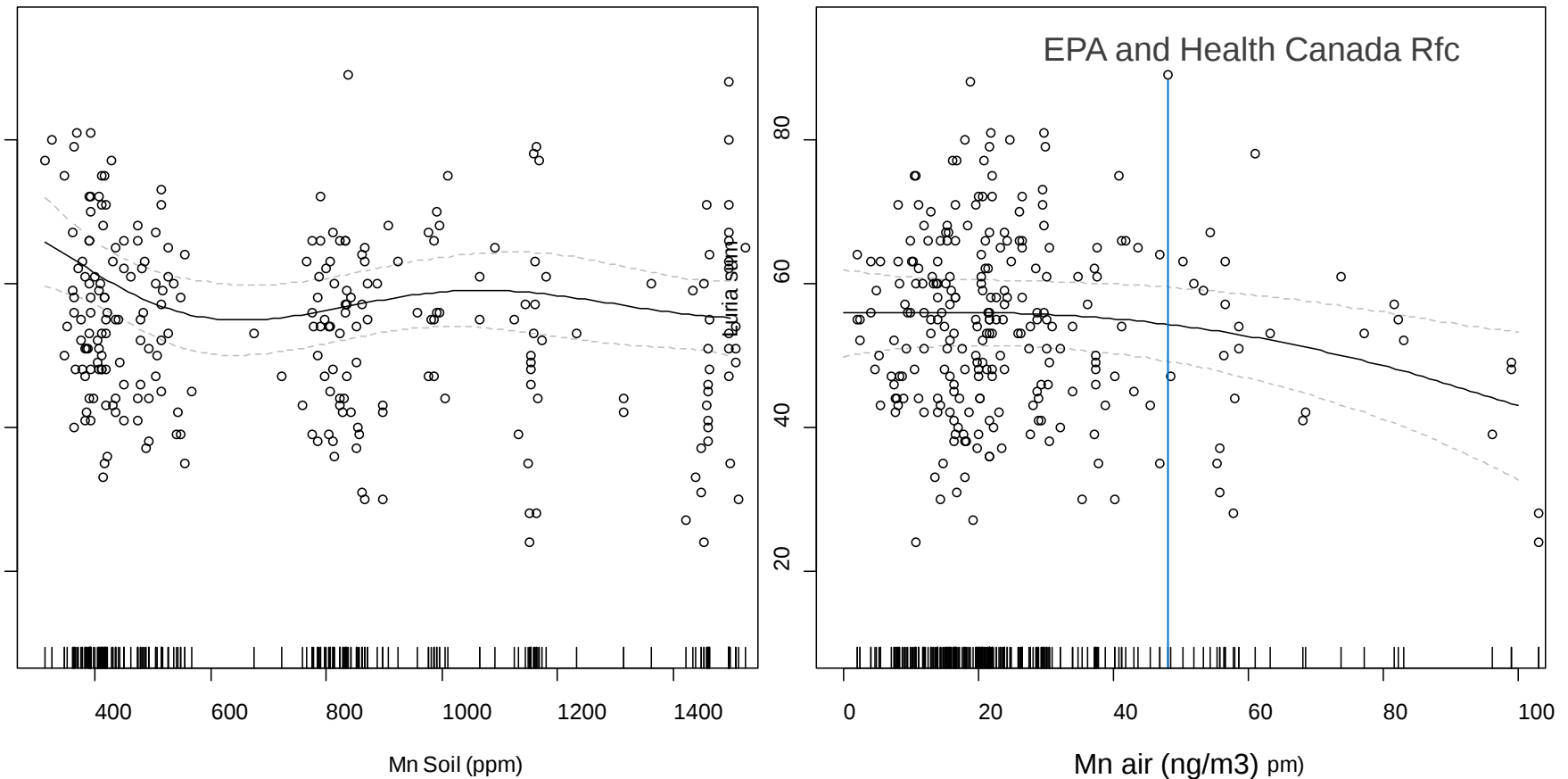
- WHO 100
- EPA 50
- Health Canada 50



Elderly



Motor coordination

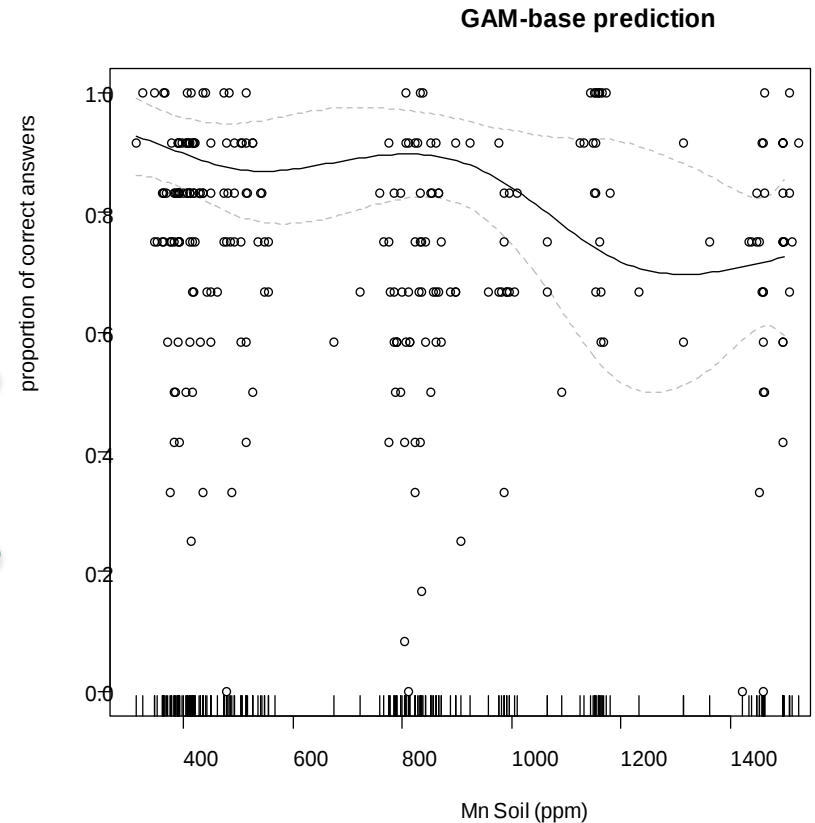


Lucchini RG et al. Neurofunctional Dopaminergic impairment in elderly after lifetime exposure to manganese. *Neurotoxicol* 2014;45:309-17

Olfactory discrimination

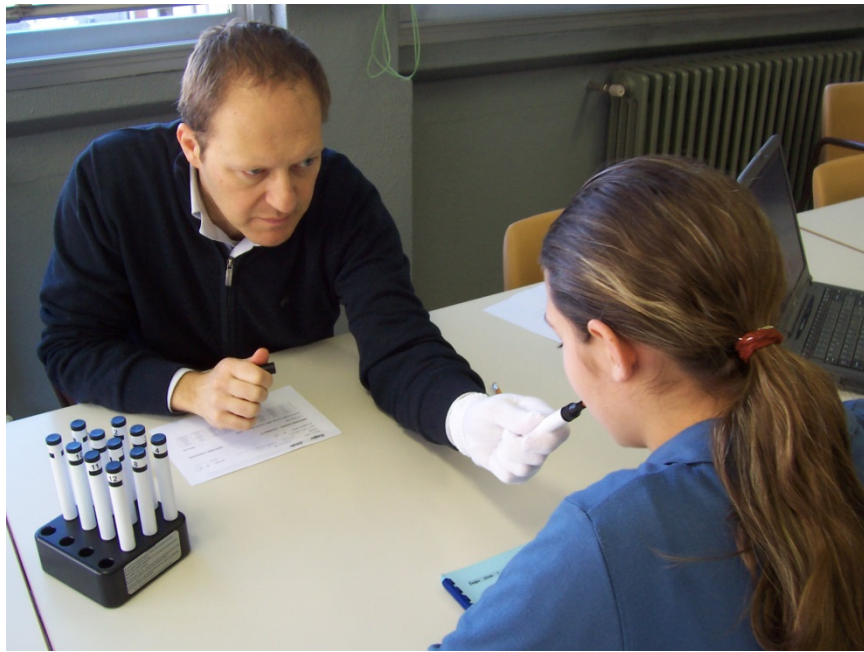
<i>Parametric:</i>	<i>Estimate</i>	<i>Std. Error</i>	<i>z value</i>	<i>Pr(> z)</i>
(Intercept)	1.4153	0.1738	8.144	0.0000
Smoke	-0.4189	0.2531	-1.656	0.0978
Gender	-0.1899	0.2132	-0.891	0.3732
Non parametric	edf	Ref.df	Chi.sq	p
s(MnSoil)	3.886	4.734	18.623	0.0018
s(log(PM10))	1.000	1.000	0.589	0.4428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



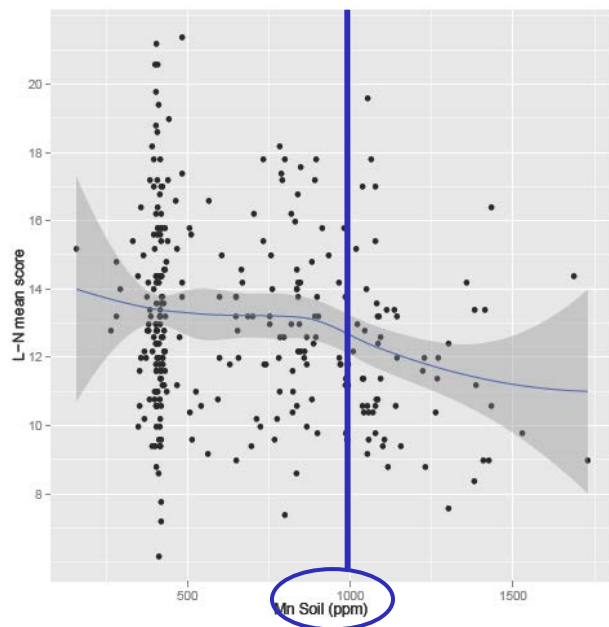
Adolescents



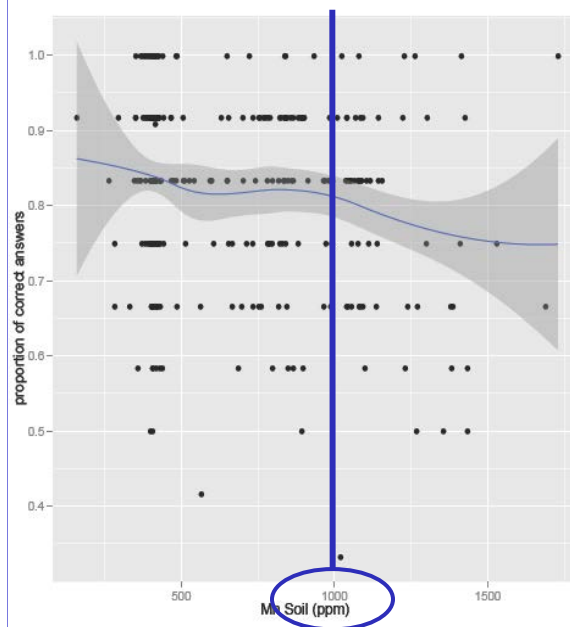


Motor/odor effects in adolescents

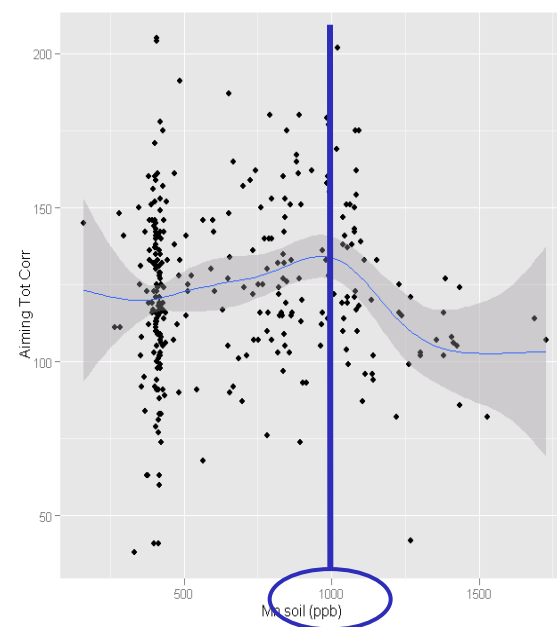
Motor Coordination



Odor identification



Hand steadiness

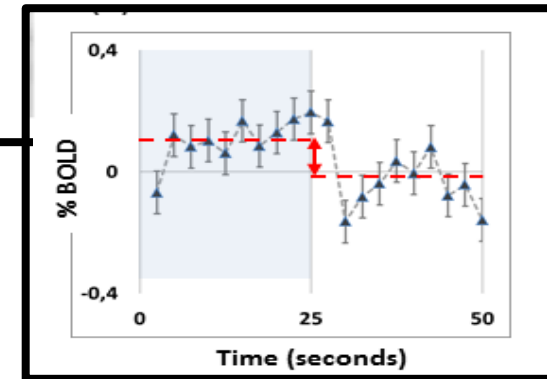
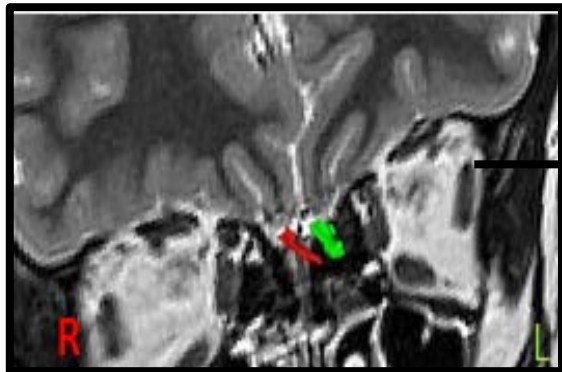


Cut-off soil Mn ~1000 ppm

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

fMRI after olfactory stimulation

	OB * volume mm ³	BOLD %	Odor intensity rating
Exposed (n=10)	115.5	37	5.25
Controls (n=4)	146.5	48	7



Iannilli et al. Effects of Manganese exposure on olfactory functions in teenagers: a pilot study. PLoS One. 2016 Jan 14;11(1):e0144783.

Genetic influence



SLC30A10

- A new transporter for Mn
- Homozygous mutation leads to hypermanganesemia, polycythemia, liver failure, Parkinsonism
- Highest expression in globus pallidus, subthalamic nucleus, bone marrow and liver

Quadri et al. Mutations in SLC30A10 cause parkinsonism and dystonia with hypermanganesemia, polycythemia, and chronic liver disease.

Am J Hum Genet. 2012 Mar 9;90(3):467-77.



Frequency of SLC30 SNPs

Frequency in the EU

- Rs1776029 allele frequency of minor allele (A) = 21%
Genotype frequencies = 4.8% for AA, 32.4% for AG, 62.8% for GG
- Rs12064812 allele frequency of minor allele (C)=30%
Genotype frequencies = 9.3% for CC, 41.4% for CT and 49.3 for TT

Frequencies for other part of the world and specific areas in Europe:

http://www.ensembl.org/Homo_sapiens/Variation/Population?db=core;r=1:219906186-219907186;v=rs1776029;vdb=variation;vf=1227868

http://www.ensembl.org/Homo_sapiens/Variation/Population?db=core;r=1:219924518-219925518;v=rs12064812;vdb=variation;vf=7234305

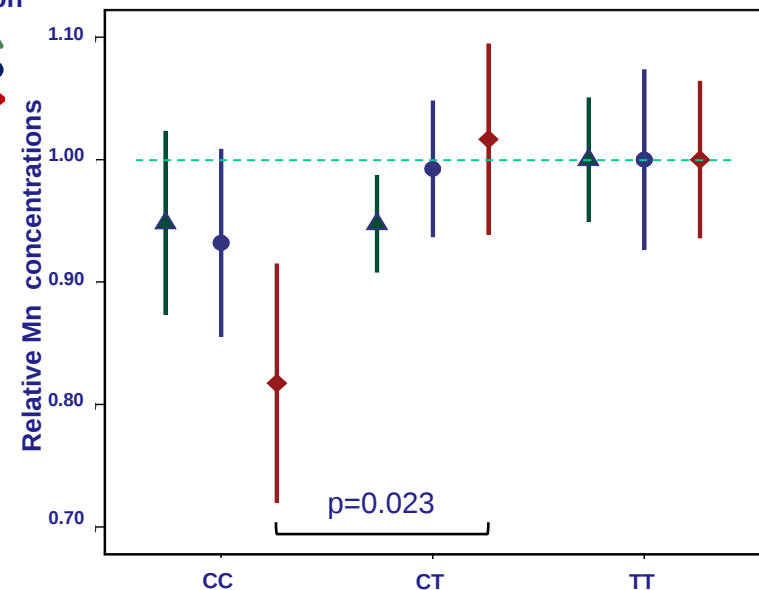
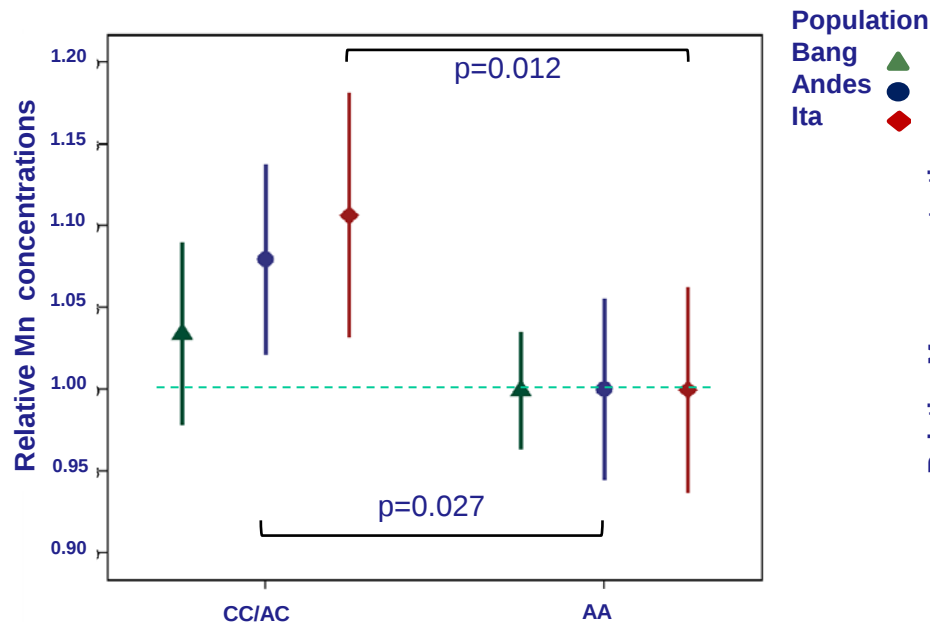
Influence of SLC30A10 on elderly

rs2275707 associates with:

- increased blood Mn
- increased sway velocity

rs12064812 associates with:

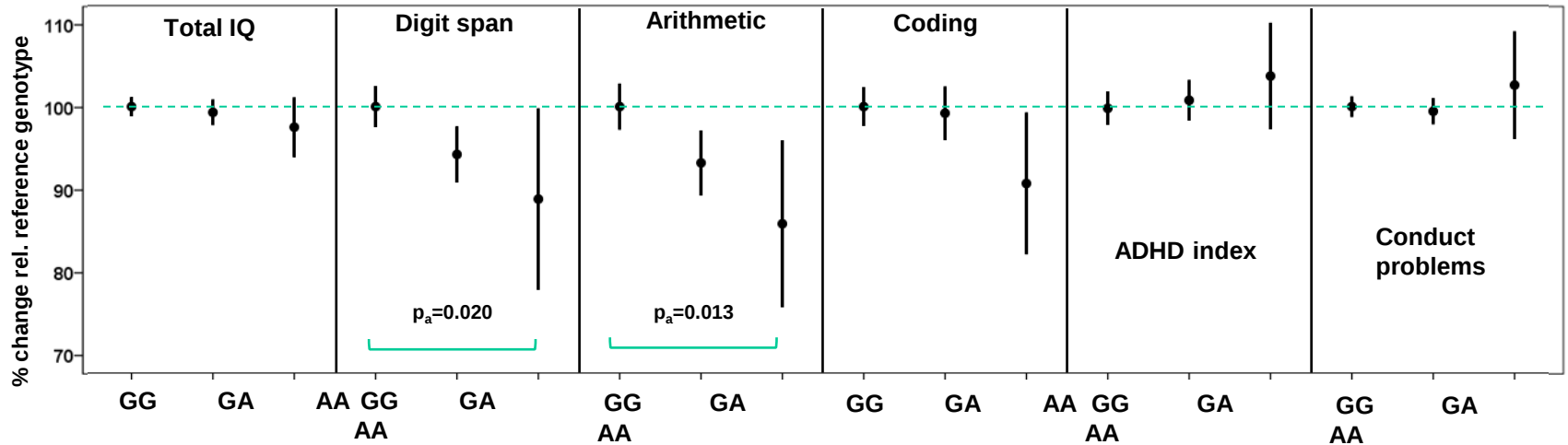
- reduced blood Mn
- increased finger tapping velocity



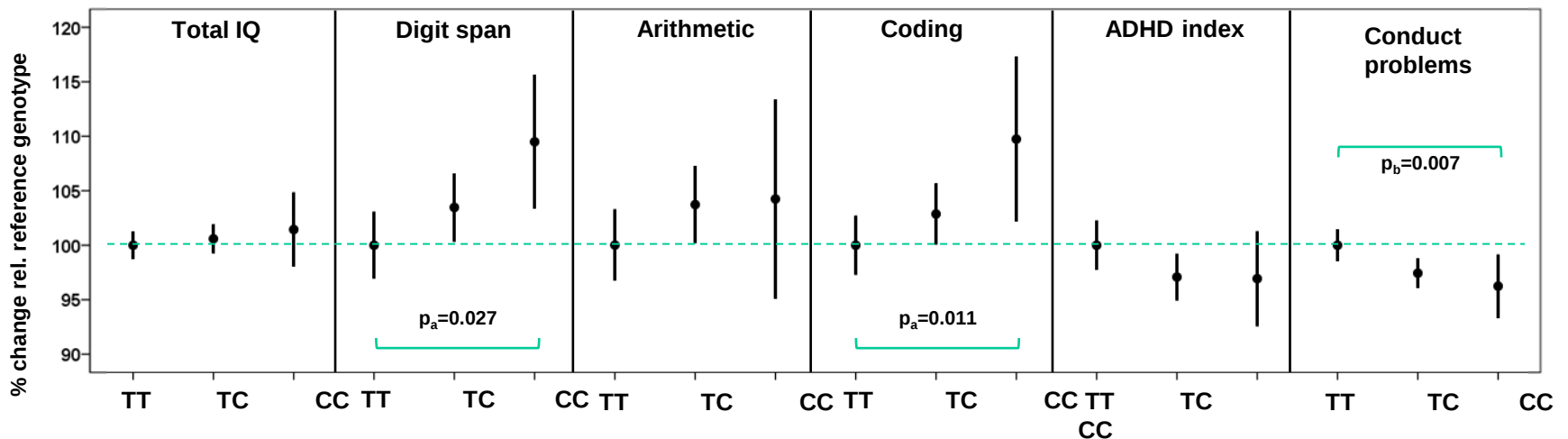
Wahlberg K et al. Common polymorphisms in the solute carrier SLC30A10 are associated with blood manganese and neurological function. *Toxicological Sciences* 2016;149(2):473-83

Influence of SLC30A10 on children

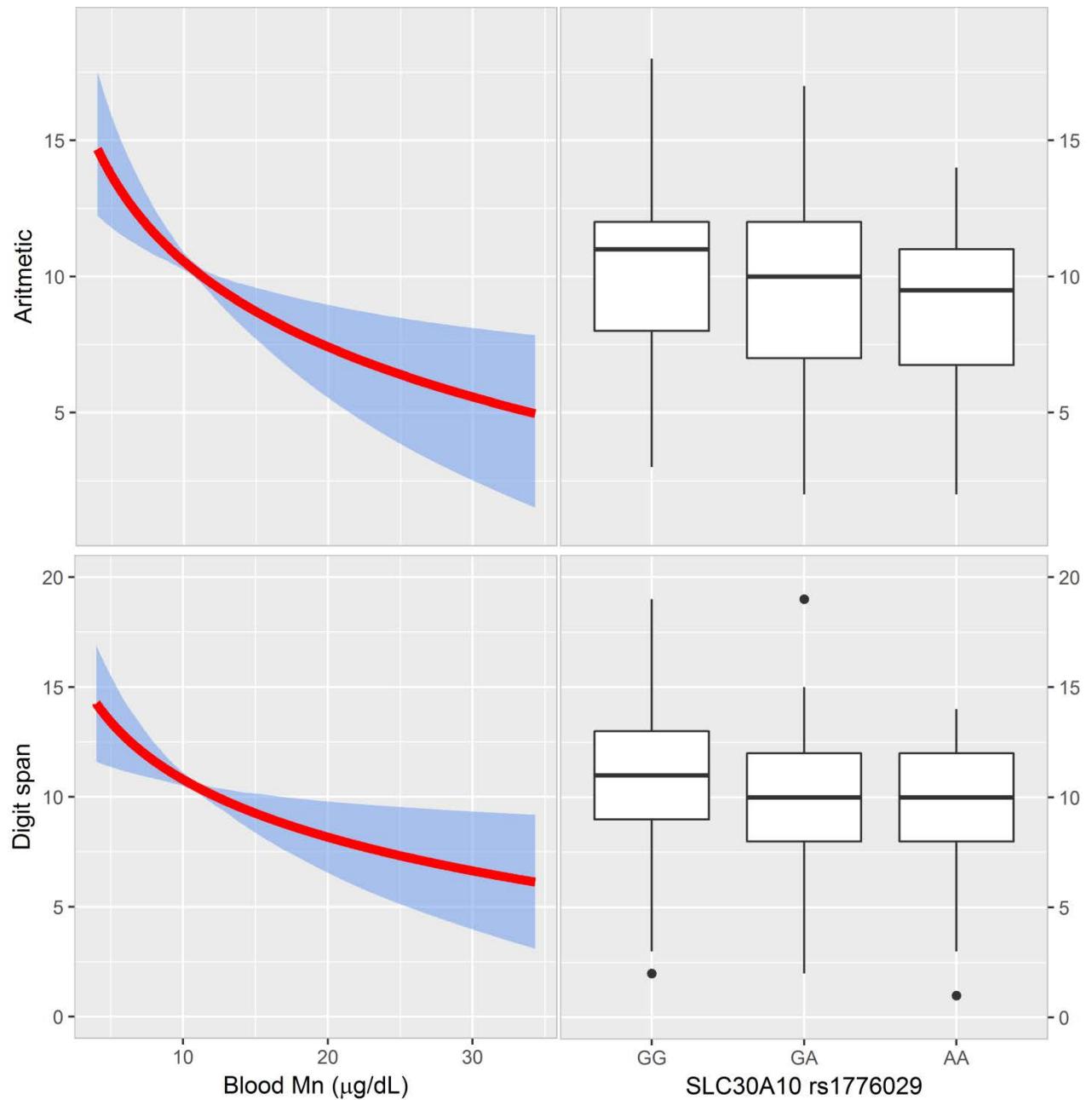
rs1776029



rs12064812



Instrument variable models

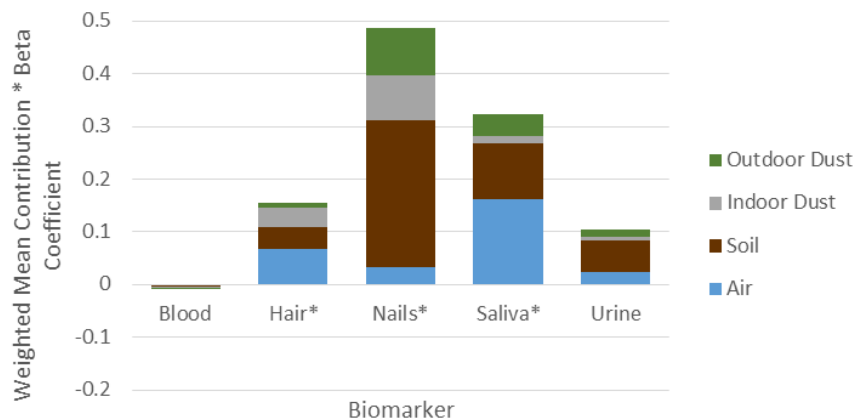


(Preliminary unpublished data)

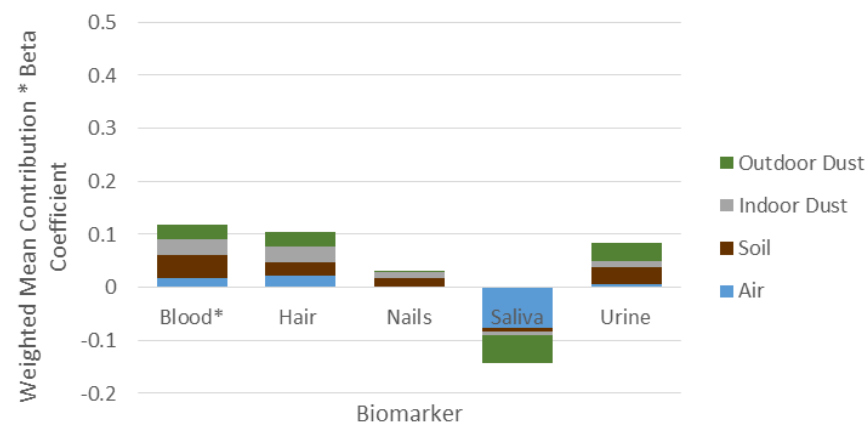
Next studies

Weighted Quantile Regression models

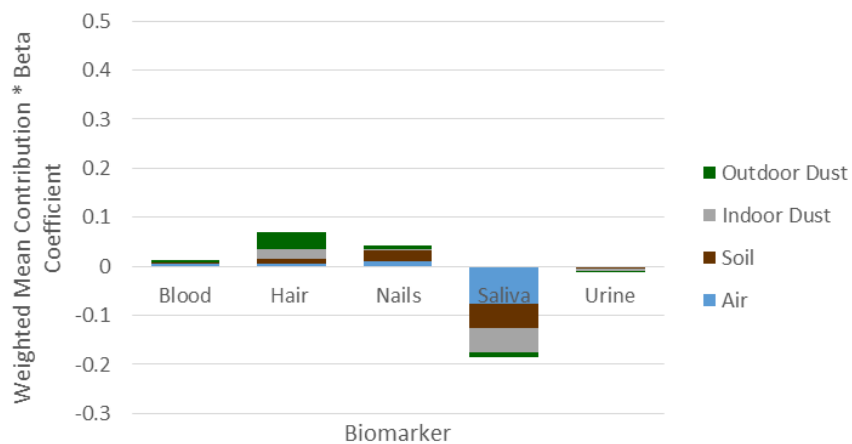
Manganese WQSR Results



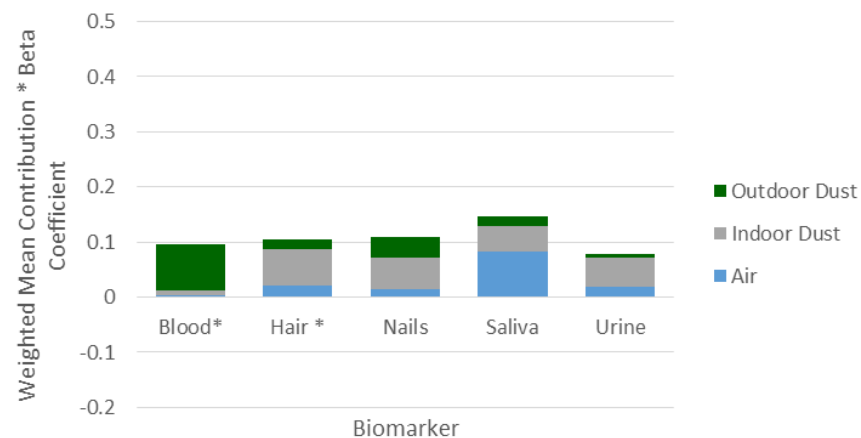
Lead WQSR Results



Copper WQSR Results

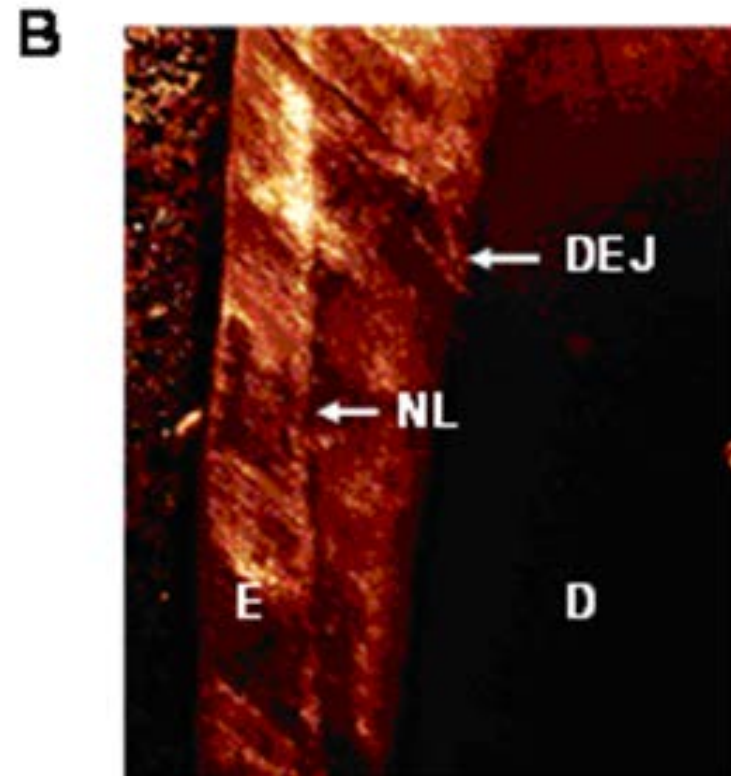
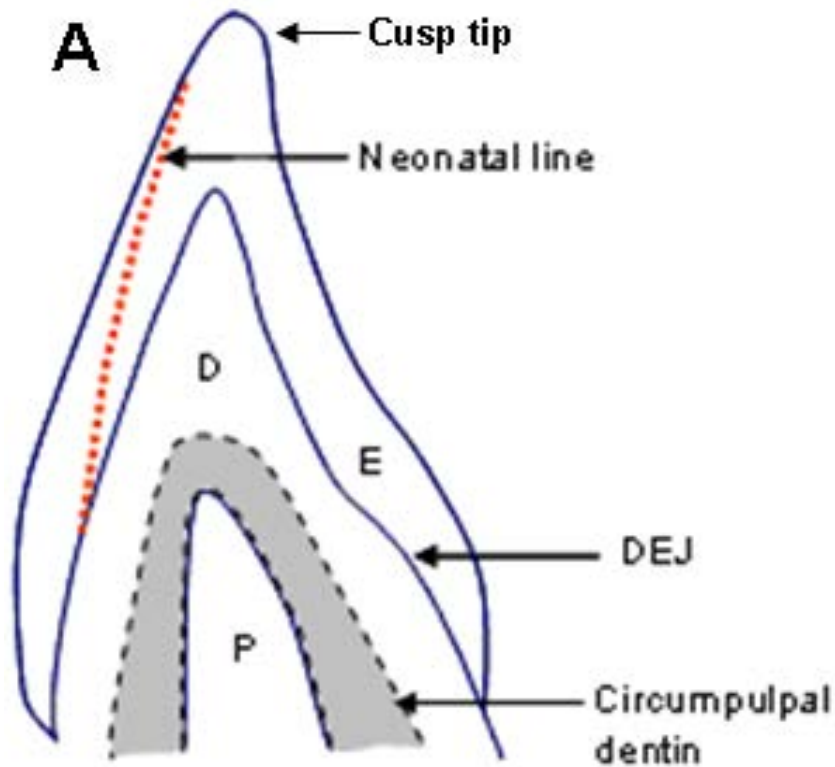


Chromium WQSR Results



(Preliminary unpublished data)

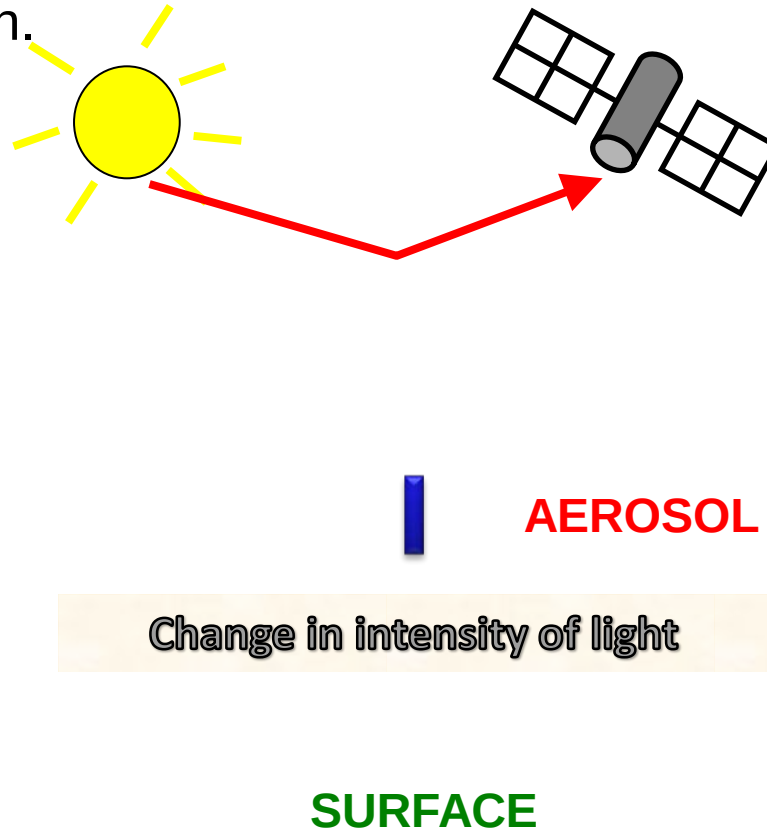
Teeth analysis

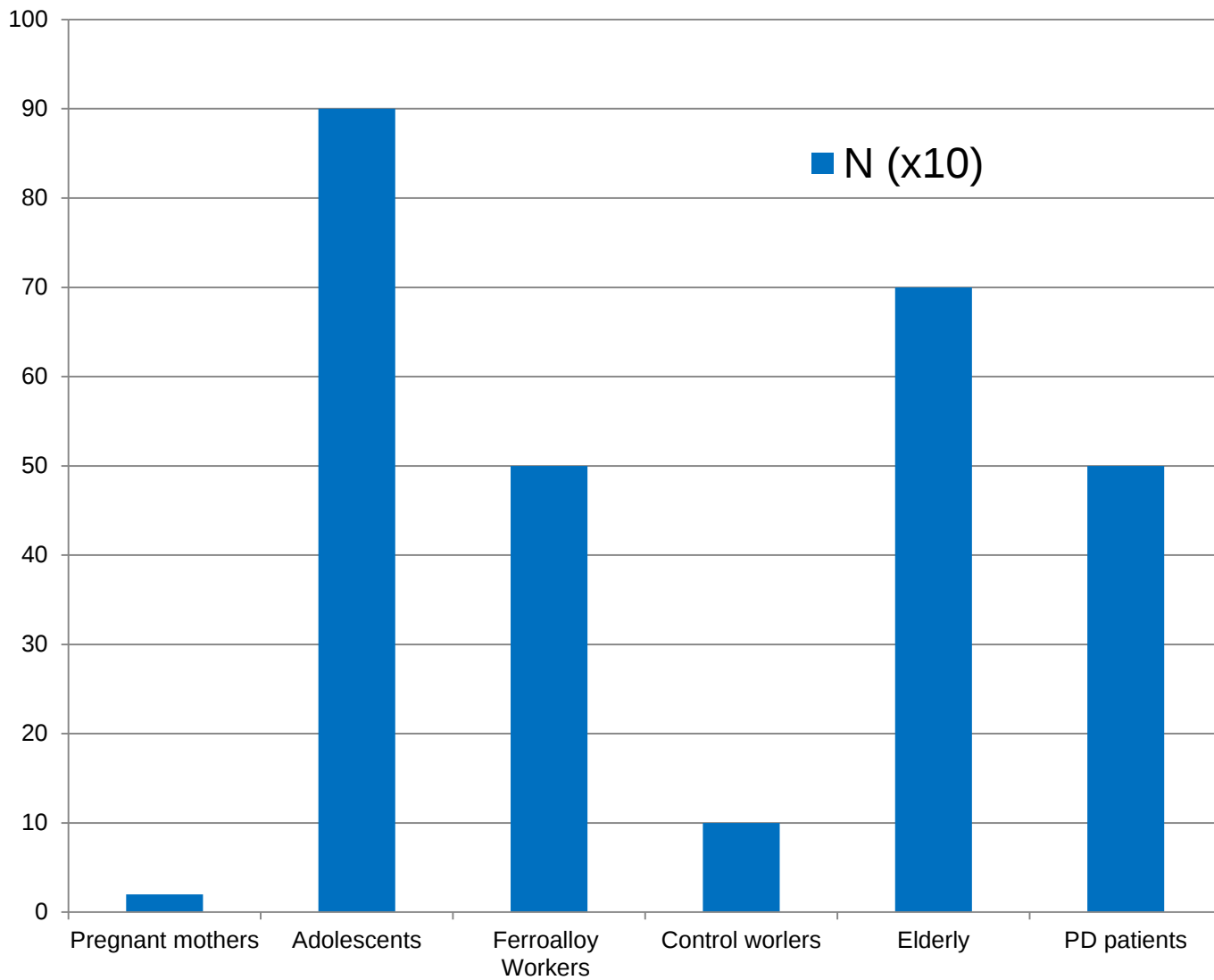


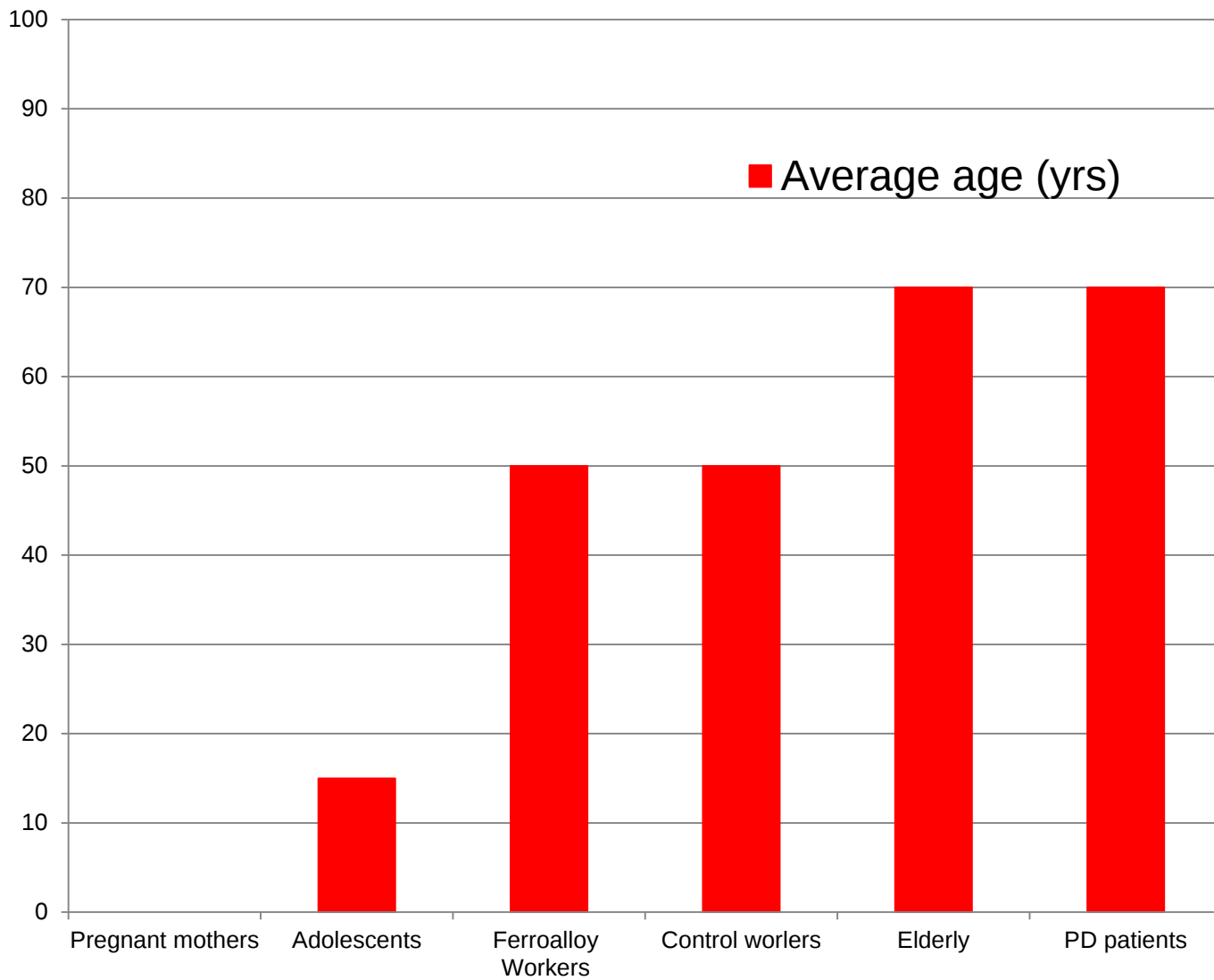
Andra SS, Austin C, Arora M. The tooth exposome in children's health research. Curr Opin Pediatr. 2016 Apr;28(2):221-7

Aerosol optical Depth: Definition

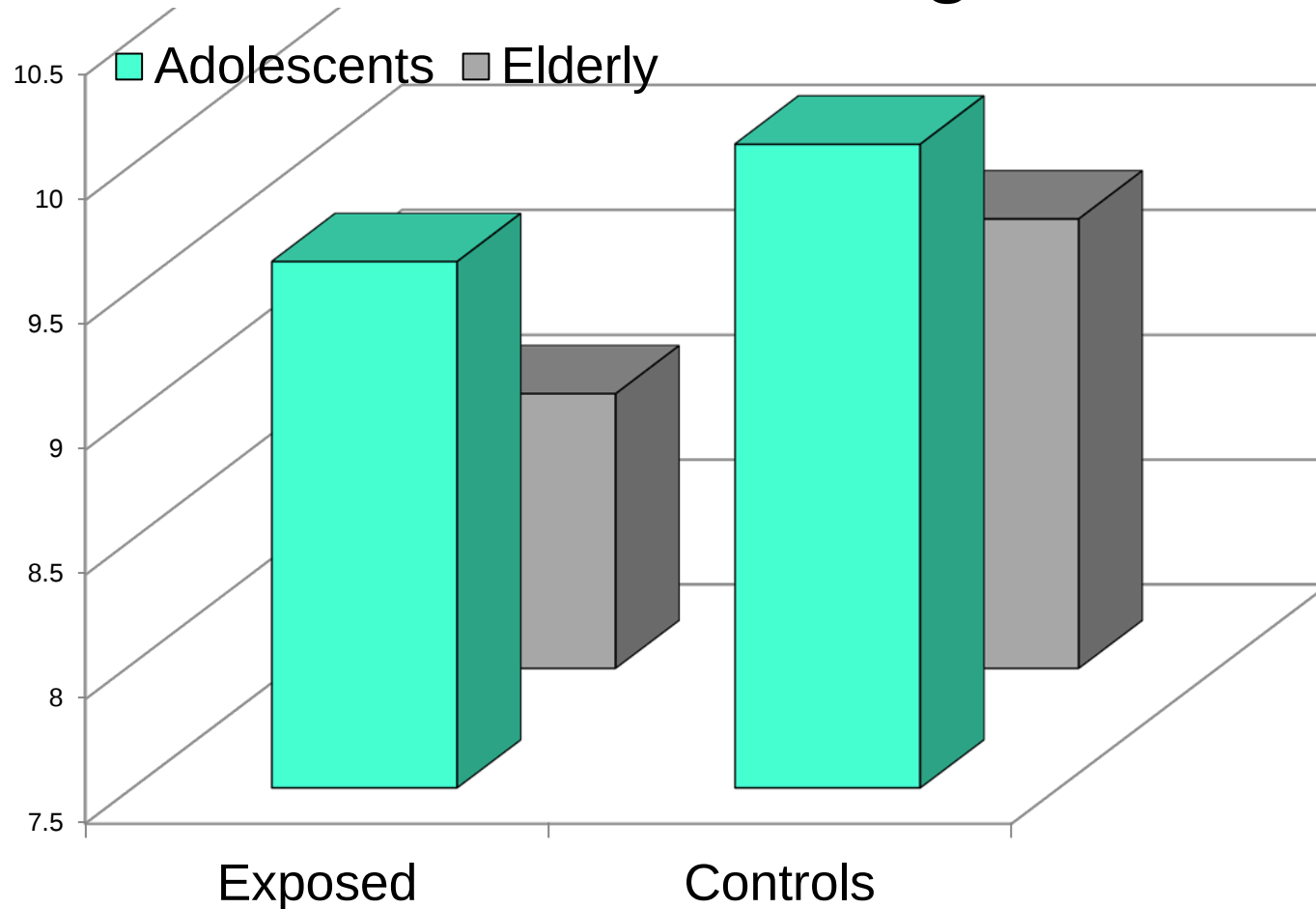
"Aerosol Optical Depth" (AOD) or "Aerosol Optical Thickness"- measures the light extinction by aerosol scattering and its absorption in the atmospheric column.







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.

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Thankyou!

For more information, to submit abstracts, and to register visit:
<http://events.mountsinaihealth.org/event/manganese2016>

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International Neurotoxicology Conference

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