Possible associations between autism spectrum disorders and environmental exposures to hazardous air pollutants:

Concentrations of Metals Potentially Relevant to Autism


<table>
<thead>
<tr>
<th>Metal</th>
<th>Suspected neurologic toxicant</th>
<th>Recognized developmental toxicant</th>
<th>Suspected endocrine toxicant</th>
<th>Cases</th>
<th>Controls</th>
<th>Mean ± SD (mcg/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>0.009 ± 0.011</td>
<td>0.008 ± 0.009</td>
<td></td>
</tr>
<tr>
<td>Manganese</td>
<td>x</td>
<td></td>
<td></td>
<td>0.003 ± 0.001</td>
<td>0.003 ± 0.001</td>
<td></td>
</tr>
<tr>
<td>Mercury</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>0.0008 ± 0.0019</td>
<td>0.0006 ± 0.001</td>
<td></td>
</tr>
</tbody>
</table>
Possible associations between Neurological disorders and environmental toxicants:

Strategies for addressing this question:

a. Clinical Observations - Case Reports
b. Basic Studies on Mechanisms of Neurotoxicity
c. Epidemiological field studies on the effects of low-level long-term exposure
d. Interdisciplinary Studies on Association between Atmospheric Levels of Toxicant and Biological Markers
ERETHISM

Hg$^0$ Neurotoxicity
The enigma of parkinsonism in chronic borderline mercury intoxication, resolved by challenge with penicillamine

Y. Finkelstein, J. Vardi, M. M. Kesten, I. Hod

Unit and Service of Neurology and Toxicology, Shaare Zedek Medical Center

Jerusalem, Israel
A 47 year old female dentist suffered from Parkinsonism

A baseline quantitative urinary mercury excretion was 46 micrograms/day

The patient was treated with chelating agent d-penicillamine for a week. Chelation therapy resulted in clinical improvement of Parkinsonism and in dynamic changes in daily urinary mercury excretion

This case may be evidence, therefore, of a rare clinical variant of elemental mercury intoxication associated with Parkinsonism, in the absence of most classical neuropsychiatric signs of chronic mercurialism
Possible associations between Neurological disorders and environmental toxicants:

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Modulation of cholinergic systems by manganese

Yoram Finkelstein a,b,*, Dejan Milatovic b, Michael Aschner b

a Unit and Service of Neurology and Toxicology, Shaare Zedek Medical Center, Jerusalem, Israel
b Department of Pediatrics and the Kennedy Center for Research on Human Development, Vanderbilt University Medical Center, Nashville, TN, USA
Locura Manganica
Manganism - Extrapyramidal stage

The organic mental syndrome is usually followed by disturbances of gait and excessive salivation, as the first manifestations of a movement disorder: an extrapyramidal syndrome clinically resembling Parkinson's Disease.
Glial targets for manganese activity:

Manganese exerts its effect on the highly dynamic reciprocal relationship between astrocytes and cholinergic neurons.
ACh

HIPPOCAMPUS

ACh

PEPTIDES
ENDOPHINES
5 - HT

MEDIAL SEPTUM

GABA

LATERAL SEPTUM

GABA

DOPAMINE
A - 10

LATERAL SEPTUM
Differential Deposition of Manganese in the Rat Brain Following Subchronic Exposure to Manganese: a T1-Weighted Magnetic Resonance Imaging Study

Yoram Finkelstein¹, Na Zhang³,⁹, Vanessa A. Fitsanakis², Malcolm J. Avison⁴-⁶,⁹, John C. Gore³,⁴,⁶,⁷,⁹ and Michael Aschner⁵,⁸,¹⁰,¹¹

¹Neurology and Toxicology Unit and Service, Shaare Zedek Medical Center, Jerusalem, Israel
²Department of Biology, King College, Bristol; and Departments of ³Physics & Astronomy, ⁴Radiology & Radiological Sciences,
⁵Pharmacology, ⁶Neurology, ⁷Biomedical Engineering, ⁸Molecular Physiology & Biophysics and ⁹Pediatrics, ¹⁰Institute of Imaging Science, ¹¹Center for Molecular Neuroscience and ¹²Center of Molecular Toxicology, Vanderbilt University, Nashville, TN, USA
Differential Deposition of Manganese in the Rat Brain
Differential Deposition of Manganese in the Rat Brain
Anatomical selectivity of manganese-induced cholinergic effects is compatible with the clinical correlates of manganism, involving:

impairment of emotional response, decline in higher cortical functions and movement disorder

Full-length review

Low-level lead-induced neurotoxicity in children: an update on central nervous system effects

Yoram Finkelstein a, Morri E. Markowitz b, John F. Rosen b

a Department of Neurology, Shaare Zedek Medical Center, Jerusalem, Israel

b Division of Environmental Sciences, Department of Pediatrics, Albert Einstein College of Medicine, Montifiore Medical Center, Bronx, NY, USA
READING AND MATH
N=4853; 6-16 Year old; Mean Blood Lead=1.9 mcg/DL

For every 1 mcg/dL increase in Blood Lead Level:

- 1 POINT IN READING
-.7 POINT IN MATH
-.1 POINT IN REASONING
-.5 POINT IN SHORT TERM MEMORY

DEFICITS OBSERVED AT LOW BLOOD LEAD LEVELS <5 mcg/dL

Lanphear, Pub Health Reports 2000
Lead and Behavior

Yule 1983: n=166, 6-12 y, Lead Blood Level: 7-32 mcg/dL

Teacher's Rating Scale (Rutter):
- Squirming, fights, thumb sucking

Conners’ Scale:
- conduct problem, inattention

Winnecke 1994: n=367, 6 y, Lead Blood Level: 1-19 mcg/dL

Tapping: max. # taps of index finger/10 sec

Pattern recognition

Jigsaw pattern identification
LEAD NEUROTOXICITY:
INTRACELLULAR MECHANISMS
Possible associations between Neurological disorders and environmental toxicants:

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d. Interdisciplinary Studies on Association between Atmospheric Levels of Toxicant and Biological Markers
Long-Term Community Exposure to Drift-Containing Organophosphate Pesticides – Are there Neurobehavioral Effects in Children?

1Yoram Finkelstein MD, PhD, 1 Amit Ophir, MSc, 3 Michael Aschner, PhD and 2 Elihu D. Richter, MD, MPH

1Service and Unit of Neurology and Toxicology, Shaare Zedek Medical Center, Jerusalem, Israel

2Dept of Occupational and Environmental Medicine, the Hebrew University School of Medicine, Jerusalem, and

3Department of Pediatrics, the Vanderbilt University Medical Center, Nashville, TN, USA
Examine the neurobehavioral status, cognition skills and task performance in schoolchildren in a rural area

A control group: Schoolchildren in kibbutzim in another area who, in all likelihood, are not exposed to pesticide drifts
Interview Questionnaires - preliminary observation:

24 out of the 60 (40%) respondents in the study group reported that at least one of their children had been diagnosed with Attention Deficit/Hyperactivity Disorder (ADD/ADHD)

ADD/ADHD Prevalence in Children in Israel and Elsewhere:

- No data exist in the Israel Central Bureau of Statistics
- A few have suggested that ADD/ADHD affects 5%-7% of the children in Israel
- Elsewhere: ADD/ADHD affects 5%-9% of the children
## ADD/ADHD in Children

<table>
<thead>
<tr>
<th></th>
<th>VALLEY</th>
<th>MOUNTAIN</th>
<th>CONTROL</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADD/ADHD</strong></td>
<td>13 (40%)</td>
<td>4 (19%)</td>
<td>3 (15%)</td>
<td>20</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>32</td>
<td>21</td>
<td>19</td>
<td>72</td>
</tr>
</tbody>
</table>
This finding raises concern, as current theory suggests that a genetic factor is primarily responsible for the pathogenesis of ADHD.
Low Level Long Term Exposure to OP Pesticides

Adding novel parameters, including

PON-1 (paraoxonase-1)

– a genetic parameter of polymorphism

Adults: blood test

Children: buccal smear
Possible associations between Neurological disorders and environmental toxicants:

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d. Interdisciplinary Studies on Association between Atmospheric Levels of Toxicant and Biological Markers
Neurological changes in children induced by sprayed organophosphorous pesticides and the atmospheric variables contributing to it

Yoram Finkelstein, Yael Dubowski, Amit Ophir, Ohad Zivan, Michael Aschner, Michal Segal-Rosenhaimer, Igal Bar-Ilan, Elyakim Doitsch and Elihu D. Richter
Precautionary Measures:

- Education
- Prevention
Impact of integrated pest management (IPM) training on reducing pesticide exposure in Illinois childcare centers

Debby F. Mir\textsuperscript{a}, Yoram Finkelstein\textsuperscript{b}, Gayle D. Tulipano\textsuperscript{c}

\textsuperscript{a} Tel Hai Academic College – Department of Environmental Sciences, Israel

\textsuperscript{b} Shaare Zedek Medical Center – Unit and Service of Neurology and Toxicology, Jerusalem, Israel

\textsuperscript{c} Northeastern Illinois University (NEIU) – Department of Geography and Environmental Studies, Chicago, USA
## New Actions Taken at Childcare Centers following IPM Training

<table>
<thead>
<tr>
<th>Program Management</th>
<th>% Uptake</th>
<th>Pesticide Practices</th>
<th>(%) Uptake</th>
<th>Preventative Measures</th>
<th>(%) Uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assigned an IPM Coordinator</td>
<td>32</td>
<td>Stopped spraying</td>
<td>27</td>
<td>Clean behind appliances</td>
<td>56</td>
</tr>
<tr>
<td>Use pest sighting logs</td>
<td>32</td>
<td>Stopped using all pesticides</td>
<td>13</td>
<td>Install door sweeps</td>
<td>30</td>
</tr>
<tr>
<td>Use monitor traps</td>
<td>29</td>
<td>Use baits instead of sprays</td>
<td>41</td>
<td>Patch holes around pipes</td>
<td>60</td>
</tr>
<tr>
<td>Create notification procedures</td>
<td>28</td>
<td>Notify parents before spraying</td>
<td>31</td>
<td>Control clutter</td>
<td>60</td>
</tr>
<tr>
<td>No change</td>
<td>19</td>
<td>No change</td>
<td>23</td>
<td>No change</td>
<td>14</td>
</tr>
</tbody>
</table>
Precautionary Measures:

- Education
- Prevention
Cotton yield Vs pesticide use in Israel

Richter et al, 1998
A fence at the top of the cliff is better than an ambulance at the bottom.

“......If not now, when...”
We are indebted to:

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The Chief Scientist, Israel Ministry of Environmental Protection

The Chief Scientist, Israel Ministry of Industry,

Trade and Labor Committee for Preventive Activity and Research in Health and Safety at Work