Environmental Health in Israel 2017: Progress and Challenges

When Environmental Chemicals Act Like Uncontrolled Medicine

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Modern Medicine is *incredibly* good at *treating* disease and *improving* the quality of *Life*.
Our Environment is *incredibly* good at *causing* disease and *diminishing* the quality of *Life*.
What is our environment?

- Microbiome
- Agricultural Chemicals, Pesticides, and Cleaners
- Water, Air, and Soil
- Prescription Drugs
- Cosmetics
- Infectious Agents
- Synthetic Materials
- Food
- Stress
- Life Style
Obesity in the US

Figure 4. Measured overweight (including obesity) among children aged 5-17, 2010 or nearest year

Source: International Association for the Study of Obesity, 2013; Bös et al. (2004), Universität Karlsruhe and Ministères de l’Education nationale et de la Santé for Luxembourg; and KNHANES 2011 for Korea.
Obesity in Israel

Data from GDB 2017 NEJM

(OECD 2011)

(Data from GDB 2017 NEJM)
OBESITY: Health Impacts

![Graphs showing disability-adjusted life-years and deaths due to obesity-related conditions over time.](image-url)
Why are we fat?

But that’s not the whole story…

Increased calorie storage
Food Preferences
Satiety
Decreased Activity
Emotional Links to Food
Difficulty losing weight with exercise
Predisposition to weight gain
The Endocrine System

• Extremely complex, many controls, interacting parts

• Multiple points of regulation for finely-tuned responses

• Sensitive to perturbations

• Naturally operates at low doses

• Effects can be activational and/or organizational
Figure 6

Endocrine Disrupting Chemicals
Biological Impacts on Human Health

- Immune function and Disease
- Reproductive Health
- Thyroid-related Disorders
- Metabolic Disorders
- Bone Disorders
- Hormone Related Cancers
- Neurodevelopmental disorders in children

Source: State of the Science of Endocrine Disrupting Chemicals – 2012
Inter-Organization Programme for the Sound Management of Chemicals
Metabolism is controlled by the endocrine system. Thus it is sensitive to disruption by endocrine disrupting chemicals (obesogens).

Badman and Flier, Science, 2005
The same pathways targeted by pharmaceuticals are altered by environmental chemicals, in an uncontrolled way.
BPA reported to impact many pathways related to obesity

- Liver: Increase in glucose, decrease in glycogen, decrease in insulin receptors and signaling.
- Pancreas: Increase in insulin production and release.
- Muscle: Decrease in glucose utilization, decrease in insulin sensitivity.
- Adipose Tissue: Increase in leptin, decrease in adiponectin, decrease in glucose utilization, increase in fatty acids accumulation.
- Hypothalamus: Decrease in POMC, increase in NPY/AgRP.

Menale et al. Open Biotech Journal 2017
Developmental Exposure to BPA Results in Weight Gain

CD-1 mice
Females Exposed Perinatally and Peripubertally

Body Weights

Animal Studies
Multiple labs
Multiple species
Sex differences
Dose range
(10ug/kg-70ug/kg)

Human Studies ?

Bisphenol A and Diabetes / Obesity (Human Studies)

- BPA and Diabetes, Glucose Homeostasis, Obesity
  - NTP Review of 8 Studies
  - Studies range from 2008 – 2011
  - Risk Estimates show:
    - All Odds Ratios > 1.00 for diabetes
    - All OR > 1.00 for glucose homeostasis
    - All OR > 1.00 for overweight & obesity
    - No pooled OR available yet
### Bisphenol A and Obesity in Children

#### Table 2. Association of Urinary Bisphenol A Concentration and Odds and Prevalence of Obesity in Strata Defined by Sample Characteristics

<table>
<thead>
<tr>
<th>Unweighted No., Obese/Total</th>
<th>Obese in Stratum, % (SE)</th>
<th>Prevalence (95% CI), %</th>
<th>OR (95% CI)</th>
<th>Prevalence (95% CI), %</th>
<th>OR (95% CI)</th>
<th>Prevalence (95% CI), %</th>
<th>OR (95% CI)</th>
<th>Prevalence (95% CI), %</th>
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</thead>
<tbody>
<tr>
<td>All</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>n = 685</td>
<td>100/2816</td>
<td>17.8 (1.3)</td>
<td>2.22</td>
<td>(1.53-3.23)</td>
<td>2.09</td>
<td>(1.48-2.95)</td>
<td>2.53</td>
<td>(1.72-3.74)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Female</td>
<td>285/1366</td>
<td>16.5 (1.5)</td>
<td>10.8</td>
<td>(6.7-14.8)</td>
<td>1.86</td>
<td>(1.10-3.17)</td>
<td>1.65</td>
<td>(0.93-2.92)</td>
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<tr>
<td>Male</td>
<td>305/1450</td>
<td>19.0 (1.8)</td>
<td>9.4</td>
<td>(6.5-12.4)</td>
<td>2.63</td>
<td>(1.56-4.43)</td>
<td>2.56</td>
<td>(1.66-3.96)</td>
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<tr>
<td>Age group, y</td>
<td></td>
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<td></td>
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<tr>
<td>&lt;12</td>
<td>227/1055</td>
<td>18.0 (1.6)</td>
<td>12.2</td>
<td>(6.8-17.5)</td>
<td>1.72</td>
<td>(1.05-2.81)</td>
<td>1.91</td>
<td>(1.14-3.21)</td>
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<tr>
<td>≥12</td>
<td>363/1761</td>
<td>17.6 (1.5)</td>
<td>9.6</td>
<td>(6.1-13.1)</td>
<td>2.59</td>
<td>(1.49-4.48)</td>
<td>2.14</td>
<td>(1.25-3.64)</td>
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<tr>
<td>Race/ethnicity</td>
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<tr>
<td>Hispanic</td>
<td>227/1004</td>
<td>23.2 (1.9)</td>
<td>22.4</td>
<td>(17.2-27.6)</td>
<td>1.24</td>
<td>(0.80-1.92)</td>
<td>0.94</td>
<td>(0.58-1.49)</td>
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<tr>
<td>Non-Hispanic white</td>
<td>124/787</td>
<td>15.5 (1.7)</td>
<td>4.7</td>
<td>(1.8-7.6)</td>
<td>4.32</td>
<td>(2.08-8.99)</td>
<td>4.21</td>
<td>(2.01-8.77)</td>
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<tr>
<td>Non-Hispanic black</td>
<td>216/893</td>
<td>24.5 (1.9)</td>
<td>20.8</td>
<td>(13.8-27.9)</td>
<td>20.7</td>
<td>(10.6-32.7)</td>
<td>1.38</td>
<td>(0.78-2.47)</td>
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<tr>
<td>Other</td>
<td>23/132</td>
<td>10.3 (2.9)</td>
<td>7.1</td>
<td>(2.4-16.7)</td>
<td>2.84</td>
<td>(0.64-12.4)</td>
<td>2.11</td>
<td>(0.30-14.8)</td>
</tr>
</tbody>
</table>

Tresande et al. 2012
Low Doses of BPA Increase Pancreatic Insulin

**In vitro**: Insulin content of islet cells treated with BPA for 24 hours.

**In vivo**: Insulin content of islet cells isolated from mice treated with BPA or vehicle for 4 days.

*Because of the way hormones act at low levels it is not surprising to see NMDRs

Alonso-Magdalena et al. 2008
Developmental Exposure to BPA Affects Brain Satiety Centers

Fetal BPA exposure

Appetite (NPY) neurons

Satiety (POMC) neurons

Increased Food Intake

Weight Gain

Ross and Desai Clin Obstet Gynecol. 2013
Developmental Exposure to BPA leads to Decreased Activity and Energy Expended in Females (90 days)

Johnson et al., J Dev Orig Health Dis, 2015
Prenatal exposure to PAHs is associated with obesity in childhood

Prenatal PAH Exposure Increases Offspring Weight Gain and Fat Mass

- Greater prenatal PAH exposure associated with:
  - Increased weight
  - Larger fat cells
  - Increased PPARγ expression
- Similar effects observed in F2 generation

- BALB/cByj mice
- Pregnant dam exposure
- GD0-21, 5hr/d 5d/wk
- PAH replicates human mixture
- Body composition
- Fat tissue analysis
- Gene expression
- DNA methylation
- Females mate with unexposed male to generate F2

Yan Z et al. PLOS One 2014
Proof of Concept: Effect of Maternal Smoking During Pregnancy on Childhood Weight

Risk Estimate
>25 epidemiology studies agree

von Kries et al., 2002
**Chemical Obesogens**

- Exposure to tobacco smoke in utero has been associated with obesity, hypertension, and gestational diabetes mellitus.

<table>
<thead>
<tr>
<th>Table 4. aORs for obesity, hypertension, T2DM, and GDM by in utero exposure to tobacco smoke among women, stratified by adult smoking.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcomes</strong></td>
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<tr>
<td></td>
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<tr>
<td>Before pregnancy</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>T2DM</td>
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<tr>
<td>GDM</td>
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</tbody>
</table>

\[ a \text{Adjusted for woman's age and education. All models except for obesity were also adjusted for prepregnancy BMI (kg/m}^2\). \]

\[ b \text{All models except for GDM were stratified by adult smoking before pregnancy; GDM model was stratified by adult smoking during pregnancy (n = 55,402 for nonsmokers and n = 18,250 for smokers).} \]

\[ c \text{Interaction term between in utero tobacco smoke (yes/no) and adult smoking (yes/no).} \]

Israel Air Quality

Annual PM10 Concentrations at Selected Monitoring Stations in Israel, 2000–2012

PM2.5 air pollution, mean annual exposure

Annual exposure to PM2.5 air pollution

Positive Associations between Ambient Air Pollution and T2DM


- PM$_{2.5}$
- Benzopyrene
- Lead
- Ozone
- nitric oxide
- sulfur dioxide
- organophosphates in household pesticides
- tobacco smoke
Pesticides and Diabetes

• **Agricultural Health Study**
  – 31,787 licensed pesticide applicators (97.4% male)
  – No diabetes at baseline
  – 5 year follow-up
Israeli Pesticide Usage

Source: Israeli Central Bureau of Statistics
Microbiome impacts how we process food we eat

And its heritable
Microbiome – Translational Research

Mayo Clinic and Day Two LTD.

• Developed an algorithm for predicting individualized blood glucose response to different foods based on gut microbiome information and other personal parameters

• Using microbiome data to produce individualized diet and wellness regimens for patients, which are meant to overcome the conundrum of why similar therapies work for some patients and not for others

Zeevi et al. *Cell* 2015
ANTIBIOTIC USE BY REGION IN 2010

RATES PER 1000 PEOPLE
National rate: 833
Northeast: 830
Midwest: 868
West: 638
South: 936

According to the Centers for Disease Control, this 2010 pattern—five courses of antibiotics prescribed for every six people—has been going on year after year.

https://www.youtube.com/watch?time_continue=955&v=4c4JviP0IfU
CDC Data for 2010

The resemblance between rates of obesity and of antibiotic use across the US is strikingly nonrandom.

https://www.youtube.com/watch?time_continue=955&v=4c4JviP0IfU
Antibiotic use in Israel

Davey et al. (2008) except the values attributed to Brazil (ANVISA 2006) and to Greece, Italy, USA and Bulgaria (Goossens et al. 2007)
The Perfect Storm for Obesity

Development: Environmental Chemicals & Nutrition, Stress...

- Altered "homeostatic" programming
  - Hedonic, reward pathway
  - Number of Fat cells, Fat cell function
- Energy expenditure, metabolic rate
- Inflammation
- Emotional and/or stress responses

Throughout Life: Stress on Abnormal Metabolic System (second hit!)

- Increased consumption of fat and sugar leading to "food addiction"
- Reduced Exercise, Altered Microbiome

Continued exposure to environmental chemicals, leading to more fat cells, inflammation
  - altered homeostatic and reward pathways

Epidemic of Obesity and Metabolic Diseases
Untested chemicals

- 80,000 Chemicals are currently in commerce; of which ~15,000 are of environmental concern
- Most have little or no hazard and exposure data
- Biomonitoring programs are being developed to identify what is making it into our bodies
Take Home Message:

In the same way as medicines produce effects in the endocrine system, environmental chemicals can similarly produce unwanted endocrine effects, resulting in a staggering increase in human diseases. These effects on endocrine and other physiological systems can have significant population-level impacts and thus require public health approaches to disease control.
THANK YOU!

http://www.niehs.nih.gov

You can’t change your genes, but you can change your environment.
Air pollution contributes to:

- Asthma
- COPD
- Developmental Disabilities
- Cancer
- Decreased IQ
- Behavioral Effects
- Autism
- Stroke
- Pneumonia
- Pulmonary Disease
- Lower Respiratory Infections
What’s in your Water?

PESTICIDES

PETROLEUM PRODUCTS

Microbes

PCBs

Perchlorate

Algal Blooms

POPs

PCBs

Mercury

Bacteria

Disinfection Byproducts

Lead

Trichloroethylene

Micro-Plastics

PFAS (PFOS/PFOA)
Land, soil, and sediment...

**Arsenic**

**Mercury**

**Copper**

**Bacteria**

**Dust**

**Pesticides**

**Chromium**

**Bioaccumulation**

**Metals**

**Fertilizer**

**Polycyclic Aromatic Hydrocarbons**

**Dioxin**

**Polychlorinated biphenyls (PCB)**
OBESITY: A Global Epidemic

Obesity numbers more than doubled in 73 countries since the study launch in 1980

In 2015, 107.7 million children and 603.7 million adults worldwide were obese

Although obesity rates in children remained lower than adults, they have grown at a faster rate
Lifelong Effects of Early-Life Exposures – Developmental Origins of Health and Disease
The Obesity-Breast Cancer Conundrum

Matthews and Thompson. *IJMS* 2016
Pharmacotherapeutics used in anti-obesity therapy

Central Nervous System Targets

Peripheral Targets

NIEHS Strategic Plan

Mission
The mission of the National Institute of Environmental Health Sciences is to discover how the environment affects people in order to promote healthier lives.

Vision
The vision of the National Institute of Environmental Health Sciences is to provide global leadership for innovative research that improves public health by preventing disease and disability.
Shifts in Causes of Death and Burden of Disease

Causes of Death

1990
- Non Communicable Diseases: 57%
- Communicable, maternal, perinatal, and nutritional conditions: 34%
- Injuries: 9%

2010
- Non Communicable Diseases: 65%
- Communicable, maternal, perinatal, and nutritional conditions: 25%
- Injuries: 10%

46.5 million

52.7 million


Lancet Commission on Pollution and Health Report

- Pollution related Disease is responsible for 9 million deaths worldwide (16%)

- 92% of pollution-related deaths occur in low-income and middle-income countries

- Welfare losses due to pollution are estimated to amount to $4.6 trillion per year (6.2% global economic output)

- Chemical pollution effects on human health are poorly defined and almost certainly underestimated

- Good News: much pollution can be eliminated, and pollution prevention can be highly cost-effective

Landrigan et al. Lancet. 2017
The Exposome

Define the exposome
- An untargeted (hypothesis free) assessment of the totality of environmental exposures
- External, internal, or both?

How to measure it
- New tools necessary to monitor exposure
- Can use biomonitoring or untargeted metabolomics to begin to do ‘top-down’ approach

Mixtures
- Chemical
- Non-chemical (infectious agents, diet, pyscho-social)

Microbiome

Rappaport and Smith (2010), Science, 330:460-461
In Utero Arsenic and Weight Gain in CD-1 Female Offspring

10ppb=drinking water standard
42.5ppm cancer causing dose

Rodriguez et al, EHP, 2015
Arsenic and Diabetes
Estrogen Receptor

Androgen Receptor

Glucocorticoid Receptor

Progesterone Receptor

Thyroid Receptor

Reproduction and Fertility

Sexual Differentiation

Immune Function

Brain Development

Metabolism

Puberty

Organ Development Maintenance

Cell Proliferation Maintenance
Antibiotic Resistance – From NC to Israel and Beyond

**THE RESISTANCE MOVEMENT**
Carbapenem-resistant Enterobacteriaceae have been on the move since at least 1996.

1. **2000:** Analysis of a 1996 sample from a North Carolinan hospital finds infectious *Klebsiella pneumoniae* carrying a gene called KPC that confers resistance to carbapenems.

2. **2003:** KPC-positive bacteria are found spreading rapidly through hospitals across New York City. By 2007, 21% of *Klebsiella* in the city carry the resistance gene.

3. **2005:** KPC-positive bacteria make their way from New York to several other countries, including Israel. From Israel, the bacteria travel to Italy, Colombia, the United Kingdom and Sweden.

4. **2008:** Doctors in Sweden find a new carbapenem-resistance gene, NDM. Traced back to India, NDM-positive bacteria have moved quickly.
Organotins Stimulate Fat Cell Development

**Tributyl Tin**

- PVC is up to 3% w/w (0.1 M) organotins
- TPT used as fungicide on high value crops
- Binds and activates at ppb (low nM) two nuclear receptors, RXR and PPARγ critical for adipogenesis
- TBT induced adipogenesis in cell culture models (nM)
- Prenatal TBT exposure led to weight gain in mice, in vivo

Grun et al., Molec Endocrinol, 2006
Prenatal TBT Exposure Reprograms MSCs to Become Fat Cells Instead of Bone Cells

- PPARγ controls choice between fat and bone pathways
- Strong animal data, no human data

Kirchner et al, 2010 Molecular Endocrinology 24, 526-539
Epigenetic Transgenerational Inheritance of Obesity

• **Positive results**
  – Tributyl tin (M and F)
  – DDT (M and F)
  – Hydrocarbon mixture (jet fuel) (M and F)
  – BPA DEHP, DBP (M and F)

• **Negative results**
  – Permethrin/DEET mixture
  – Vinclozolin
  – Dioxin

Exposure (F0)

Assess Weight Gain (F4)
F4 TBT Males are Resistant to Fasting-induced Fat Loss

TBT animals do not mobilize fat comparably to controls

Chamorro-Garcia et al., in preparation