PERSISTENT ORGANIC POLLUTANTS (POPs) AND METABOLIC DISORDERS (OBESITY, DIABETES)

REVIEW OF THE LITERATURE IN EPIDEMIOLOGY

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OUTLINE

General background
Epidemiology – what need to be known
Scientific background
Review of the litterature in epidemiology
Non-persistent chemicals and metabolic diseases
Conclusion
GENERAL BACKGROUND

Expertise Collective from Inserm on « pesticides and health effects », personal contribution on « pesticides and metabolic diseases »

Review of the literature in epidemiology: POPs and diabetes


Project granted by the ANR on POPs concentrations and diabetes and other metabolic disorders
WHAT NEED TO BE KNOWN

EPIDEMIOLOGY
**DEFINITION**

Epidemiology is the study of the distribution and determinants of health-related states or events (including disease), and the application of this study to the control of diseases and other health problems.

Various methods can be used to carry out epidemiological investigations: surveillance and descriptive studies can be used to study distribution; analytical studies are used to study determinants.
ECOLOGICAL STUDY

[Graph showing the relationship between lung cancer rates at age 35-44 in mid-1970s and manufactured cigarettes per adult in 1950, with countries marked for varying smoking rates and death counts.]
CROSS-SECTIONAL STUDY

At the same time

Beginning of the study, inclusion of the subjects and collect of information

Time

Fast and relatively cheap
No delay between exposure and outcome
PROSPECTIVE COHORT STUDY

Inclusion of the subjects  Collect of information

E  Latency  O

Beginning of the study

Time

Expensive
Several years of follow-up
Timing between exposure and outcomes
# MEASUREMENT ERROR

<table>
<thead>
<tr>
<th></th>
<th>E+</th>
<th>E-</th>
</tr>
</thead>
<tbody>
<tr>
<td>O+</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>O-</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

Without: \[ a+b+c+d = a' + b' + c' + d' \]

With:

Dependant of the outcome \( \Rightarrow \) non-predictable bias direction
Independant of the outcome \( \Rightarrow \) underestimate the association
CONFOUNDING FACTORS

The observed association can be due to another factor Z
- if Z is associated to E
- if Z is associated to O whatever the exposure level

\[ E \quad ? \quad O \]

\[ Z \]

e.g. Age
SCIENTIFIC BACKGROUND
METABOLIC DISEASES

Obesity, diabetes, dyslipidemia, hypo/hyperthyroïdism, etc.

Multifactorial diseases:
- genetic susceptibility
- poor diet, sedendarity, lack of physical activity, tobacco smoke

Rapid increase of these diseases during the last decades not fully explained by these lifestyle factors

⇒ suspected: chemicals, microbiote, air pollution
TYPE 2 DIABETES

- Prevalence in France: >5%
- Strong association with overweight and abdominal fat mass
- Hyperglycemia (diagnostic) and insulin resistance
- Many complications: e.g. chronic kidney disease, stroke
Adipocytes as regulators of energy balance and glucose homeostasis
Evan D. Rosen and Bruce M. Spiegelman
Nature 444, 847-853 (14 December 2006)
OBESITY PREVALENCE (IMC > 30 KG/M^2) FROM OBEPI STUDIES (FRANCE)
INCREASE IN WAIST CIRCUMFERENCE (CM)
FROM OBEPI STUDIES (FRANCE)
U.S. synthetic chemical production and diabetes prevalence.

Brian A. Neel, and Robert M. Sargis Diabetes 2011;60:1838-1848
ENDOCRINE DISRUPTING CHEMICALS

Persistent (POPs)
- Organochlorinated pesticides
- Polychlorinated biphenyls (PCBs)
- Dioxins and furans
- Perfluorinated compounds (PFCs)
- Brominated flame retardants

Not persistent
- Organophosphorus pesticides
- Bisphenols
- Parabens
- Phthalates
- TBT
- Heavy metals
Sources and targets of metabolic disruptors.

**Sources of Chemicals**
- Agriculture
- Industrial Waste
- Phytochemicals
- Pharmaceuticals
  - Consumer Products

**Routes of Exposure**
- Transdermal
- Inhalation
- Transplacental
- Ingestion

**Metabolic Targets**
- Adipose Tissue
- Pancreas
- Liver
- Brain
- Skeletal Muscle

**Pathophysiological Effects**
- Obesity
- Insulin Resistance
- Diabetes
- Hypertension
- Dyslipidemia

Brian A. Neel, and Robert M. Sargis Diabetes 2011;60:1838-1848

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# Pesticides

## Classes | Examples
--- | ---
**Organochlorinated (OC)** | aldrin, chlordane, DDT, heptachlor, lindane (γHCH), toxaphene, β/γHCH (hexachlorocyclohexane), HCB (-benzene), oxychloridan, trans-nonachlor, mirex

**Organophosphorus (OP)** | chlorpyrifos, coumaphos, diazinon, dichlorvos, fonofos, malathion, phorate, parathion, terbufos, trichlorfon

**Carbamates** | aldicarb, carbaryl, carbofuran

**Pyrethroids** | permethrin

**Fungicides** | benomyl, captan, chlorothalonyl, maneb/mancozeb, metalaxyl, ziram

**Gaseous** | carbon tetrachloride / disulfite, methylbromide

**Herbicides** | 2,4,5T, 2,4,5TP, 2,4D, alachlor, atrazine, butylate, cyanazine, paraquat, bromoxynil (phenolique), dicampa, fenoxaprop, MCPA, ethalfluralin, trialfate, trifluralin

**Herbicides contaminants** | dioxine (TCDD)
Pesticides

- Organochlorinated pesticides the most studied
- Lipophilic compounds, very resistant → persistent, bioaccumulation, forbidden in the 70's
- Exposure mainly through diet (95%)
MECHANISMS OF POPS

Not fully elucidated

TCDD $\downarrow$ glucose uptake $\rightarrow$ insulin secretion $\downarrow$

Through binding to AhR $\rightarrow$ GLUT transporter expression $\downarrow$

Other possible mechanisms:

- pancreatic NO synthase
- $\uparrow$ expression of TNF $\alpha$ (implicated in insulin-resistance)

Action as EDCs:

- via nuclear receptor (androgen, estrogen, PPAR)
POSSIBLE MECHANISMS OF OP PESTICIDES

Lasram MM et al. Toxicology. 2014
POPS AND METABOLIC DISEASES

REVIEW IN EPIDEMIOLOGY
POPS AND FAT MASS

Direction of the association not established

- Cross-sectional studies
- Lipophilic – Bioaccumulation
- Age rather than obesity due to accumulation (Hue et al, 2007)

An hypothesis: weight loss → pesticides in the bloodstream → health effects including weight regain through thermogenesis control and hypothyroïdism (Tremblay et al, 2004)
OCCUPATIONAL STUDIES

US Veterans from Vietnam war (Agent Orange, herbicide w. TCDD) Henriksen et al, 1997:
- diabetic cases had 3 times higher concentration of POPs after 10y
- those with dioxin > median had higher risk of diabetes (RR=1.5 [1.2; 2.0])

Results not confirmed in NIOSH (US workers), 15y exposure to TCDD
- possible co-exposure

Agricultural Health Study (30,000 subjects, prospective)
- 7/50 pesticides associated with 5y incidence of diabetes
- replicated for herbicides in Australia (Beard, 2003)

Pyrethroides associated to glucose deregulation in 3,000 Chinese workers (Wang, 2011)
Original Contribution


M. P. Montgomery\(^1\), F. Kamel\(^1\), T. M. Saldana\(^2\), M. C. R. Alavanja\(^3\), and D. P. Sandler\(^1\)

\(^1\) Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC.

\(^2\) Social & Scientific Systems, Durham, NC.

\(^3\) Occupational and Environmental Epidemiology Branch, National Cancer Institute, Bethesda, MD.
Prospective cohort study of pesticide applicators

N=33457 → 1176 diabetics and 30611 non diabetics

Lifetime occupational exposure (questionnaire)

7 among 50 pesticides associated with diabetes with a cumulative exposure:

- OC : aldrin, chlordane, heptachlor,
- OP : dichlorvos, trichlorfon,
- Herbicides : alachlor, cyanazine

3 are POPs

Stronger associations in obese subjects
RESULTS IN GENERAL POPULATION (NHANES)

Strong association with heptachlor, oxychlordane, intermediate for pp’DDT, low for HCB, pp’DDE and trans-nonachlor and not significant for mirex and aldrin in about 3000 subjects.

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Adjusted association of number of organochlorine pesticides elevated with total diabetes.

<table>
<thead>
<tr>
<th>Odds ratio</th>
<th>95% CI</th>
<th>Percent of sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>None of 6 pesticides elevated</td>
<td>1.00</td>
<td>–</td>
</tr>
<tr>
<td>1 of 6 pesticides elevated</td>
<td>1.30</td>
<td>0.47–3.55</td>
</tr>
<tr>
<td>2 of 6 pesticides elevated</td>
<td>1.56</td>
<td>0.64–3.81</td>
</tr>
<tr>
<td>3 of 6 pesticides elevated</td>
<td>2.05</td>
<td>0.88–4.78</td>
</tr>
<tr>
<td>4 of 6 pesticides elevated</td>
<td>3.99</td>
<td>1.47–10.86</td>
</tr>
<tr>
<td>5 of 6 pesticides elevated</td>
<td>8.15</td>
<td>3.49–19.05</td>
</tr>
<tr>
<td>6 of 6 pesticides elevated</td>
<td>8.17</td>
<td>2.56–26.09</td>
</tr>
</tbody>
</table>

*a Six organochlorine pesticides evaluated were: beta-hexachlorocyclohexane, p,p’-DDE, p,p’-DDT, oxychlordane, trans-nonachlor, and heptachlor epoxide. Logistic regression adjusted for age, gender, race/ethnicity, education, poverty income ratio, body mass index, waist circumference, physical activity, and family history of diabetes.

Everett, Environment International. 2010
<table>
<thead>
<tr>
<th>Source</th>
<th>Pesticide types</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-sectional</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Codru et al. [23]</td>
<td>M,DDE,HCB†</td>
<td>3.35 (1.16, 9.66)</td>
</tr>
<tr>
<td>Cox et al. [34]</td>
<td>HCB,TN,DDT,DDE,HCH,O,D†</td>
<td>1.80 (0.66, 4.90)</td>
</tr>
<tr>
<td>Everett et al. [17]</td>
<td>DDT†</td>
<td>2.46 (1.45, 4.18)</td>
</tr>
<tr>
<td>Jorgensen et al. [25]</td>
<td>A,M,HCB,HCH,AC,GC,TN,CN,DDT,DDE†</td>
<td>1.80 (0.59, 5.51)</td>
</tr>
<tr>
<td>Philibert et al. [27]</td>
<td>DDE§</td>
<td>3.56 (0.98, 12.98)</td>
</tr>
<tr>
<td>Son et al. [36]</td>
<td>O,TN,HE,HCB,HCH,M,DDE,DDD,DDT†</td>
<td>7.69 (1.15, 51.48)</td>
</tr>
<tr>
<td>Uкроpec et al. [29]</td>
<td>HCB,DDE,DDT,HCH**</td>
<td>1.60 (0.87, 2.94)</td>
</tr>
<tr>
<td>Airaksinen et al. [30]</td>
<td>O,TN,DDE††</td>
<td>2.01 (1.12, 3.63)</td>
</tr>
<tr>
<td>Gasull et al. [32]</td>
<td>HCB,HCH,DDT,DDE†</td>
<td>1.20 (0.54, 2.67)</td>
</tr>
<tr>
<td>Arrebola et al. [38]</td>
<td>DDE†</td>
<td>2.94 (1.02, 8.49)</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td>2.28 (1.73, 3.02)</td>
</tr>
<tr>
<td>Prospective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rignell-Hydibom et al. [24]</td>
<td>DDE§</td>
<td>5.47 (1.21, 24.76)</td>
</tr>
<tr>
<td>Turyk et al. [53]</td>
<td>DDE†</td>
<td>7.10 (1.60, 31.49)</td>
</tr>
<tr>
<td>Lee et al. [55]</td>
<td>O,TN,HCB,HCH,DDE,DDT,M†</td>
<td>1.16 (0.41, 3.28)</td>
</tr>
<tr>
<td>Lee et al. [56]</td>
<td>DDE,TN,HCB**</td>
<td>3.39 (0.99, 11.64)</td>
</tr>
<tr>
<td>Wu et al. [5] (1)</td>
<td>DDE,DDT,HCB†</td>
<td>1.58 (0.46, 5.45)</td>
</tr>
<tr>
<td>Wu et al. [5] (2)</td>
<td>DDE,DDT,HCB†</td>
<td>1.86 (0.57, 6.03)</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td>2.43 (1.39, 4.25)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>2.30 (1.81, 2.93)</td>
</tr>
</tbody>
</table>

Song Y et al. J Diabetes. 2015 - ~idem for dioxins and PCBs
Fig. 1. Adjusted odds ratios (OR) for diabetes in the tertiles (T) of adipose tissue concentration of $p,p'$-DDE and two levels of BMI.
OTHER PESTICIDES

Organophosphorus pesticide

- Neurotoxic (acetyl cholinesterase inhibitors) and endocrine disrupting compound
- A trend was observed in the Agricultural Health Study

Carbamates

- Very few data

As a shared mechanism, all OP, CB and OC induce cellular oxidative stress via affecting mitochondrial function and therefore disrupt neuronal and hormonal status of the body (Karami-Mohajeri S & Abdollahi M. Review. Hum Exp Toxicol. 2011).
NON-PERSISTENT PESTICIDES

Very few epidemiological data

No prospective cohort study

Exposure difficult to assess:

- low $t_{1/2}$

- the biomarker represent a recent exposure

**Background:** Experimental evidence suggests that developmental exposure to persistent organic pollutants (POP) and to some non persistent pesticides may disrupt metabolic regulation of glucose metabolism and insulin secretion, and thereby contribute to the current epidemic of obesity and metabolic disorders. Quasi-experimental situations of undernutrition in utero have provided some information. However, the evidence in humans concerning the role of the prenatal environment in these disorders is contradictory, and little is known about long-term outcomes, such as type 2 diabetes, of prenatal exposure.

**Objectives:** Our aim was to evaluate the effects of prenatal exposure to POP and organophosphate pesticides on fetal markers of glucose metabolism in a sample of newborns from the Pelagie mother–child cohort in Brittany (France).

**Methods:** Dialkylphosphate (DAP) metabolites of organophosphate pesticides were measured in maternal urine collected at the beginning of pregnancy. Cord blood was assayed for polychlorinated biphenyl congener 153 (PCB153), p,p’-dichlorodiphenyl dichloroethene (DDE) and other POP. Insulin and adiponectin were determined in cord blood serum (*n*=268).

**Results:** A decrease in adiponectin and insulin levels was observed with increasing levels of DDE, but only in girls and not boys. Adiponectin levels were not related to the concentrations of other POP or DAP metabolites. Decreasing insulin levels were observed with increasing PCB153 concentrations. Insulin levels increased with DAP urinary levels. Additional adjustment for BMI z-score at birth modified some of these relations.

**Conclusions:** Our observations bring support for a potential role of organophosphate pesticides and POP in alterations to glucose metabolism observable at birth.
CONCLUSION
IN SUMMARY

Many studies have shown a relationship between exposure to POPs and increase risk of diabetes and other metabolic diseases (in particular, obesity, dyslipidemia)

Few prospective cohort studies

Data rather on OC pesticides, scarce on the more recent ones that are on the market
LIMITATIONS

- Publication bias
- Mainly cross-sectional studies
- Difficulties for exposure assessment
CONCLUSION

Not specific to pesticides: Endocrine Disrupting Chemicals
(concerns about bisphenols, parabens, phthalates)

To consider:
- Windows of susceptibility: prenatal exposures (fetal programming)
- Mixture of contaminants, even at low doses