Health effects of low-level pesticide exposure in humans

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Key question

Are pesticide residues in food a health risk to the population?
Why worry?

- Pesticides are bioactive compounds designed to kill insects, plants, or fungi
- Most insecticides target the nervous system in insects – and have neurotoxic potential in other species
- Many pesticides have endocrine disrupting potential

Human health risk depends on

- Toxic properties and potency of the pesticides
- Time of exposure – sensitivity windows
- Vulnerable population groups (e.g. genetics)
- Exposure level (mixtures)
Potentials for pesticide exposure

- Widespread usage: 0.3 kg (EU) and 1 kg (US) per inhabitant per year
- Occupational and neighborhood exposures
- Pesticide residues detected in 40-50% of fruit, vegetables and cereals (EU),
- over 25% contain more than one, and some samples contain over 20 different pesticides
- Mixed exposure of the population

Acute toxicity from pesticide residues in food

- Unwell/ sick shortly after eating
  - typically gastrointestinal and neurological symptoms
- Very uncommon in the EU and the U.S.
  - a little more common in developing countries

An outbreak of illness among school children in London: toxic poisoning not mass hysteria
*Journal of Epidemiology and Community Health* 1994;48:41-45

Aldicarb as a Cause of Food Poisoning – Louisiana 1998,
*Centers for Disease Control and Prevention, Morbidity and Mortality Weekly Report, MMWR.* 1999;48:269-271
Long-term effects

Some studies find associations between
- Occupational exposure to pesticides and lymphoma/leukemia or hormone related cancers (ovarian, prostate and breast)
- Residential or parental pesticide exposure and childhood cancers (leukemia, brain cancer)
- Occupational or residential pesticide exposure and neurodegenerative diseases, e.g. Parkinson's disease and Alzheimer's disease
- Occupational pesticide exposure and reduced fertility and semen quality

High vulnerability during development - fetal and early childhood

- Developmental processes are easily disrupted during time windows of rapid growth and development
- Development occurs in a precisely timed sequence
- The nervous-, reproduction-, endocrine, and immunological systems are not fully developed at birth

Damages incurred during development are likely to be permanent and may increase the risk of dysfunction and/or disease later in life (Developmental programming)
• A child’s developing nervous system is more sensitive to chemical exposures than the adult nervous system.

Some pesticides inhibit cholinesterase and some interfere with thyroid function.
- Acetylcholin is a key neurotransmitter and a guidance substance in neuron migration during development
- Thyroid hormone is essential for brain development

• ~200 chemicals are known neurotoxic to humans
• Of these ~ 90 are pesticides
Developmental neurotoxicity of pesticides in experimental animals

Organophosphate insecticides
  chlorpyrifos, parathion, diazinon

Pyrethroid insecticides
  bioallethrin, deltamethrin, cypermethrin, fenvalerate

Dithiocarbamates fungicides
  maneb, mancozeb

Chlorophenoxy herbicides
  2,4-D

Review: Bjørling-Poulsen et al., Environmental Health 2008, 7:50

Preschool children (4 to 5-year-old) in Mexico

Similar (genetic, cultural, social, age) groups of children:
1. Low exposure (N=17)
   living in the foothills – ranching with low pesticide use
2. High exposure (N=33)
   Living in the valley – agriculture with intensive pesticide use
   Mixed pesticide exposure (mainly organophosphates and organochlorines).
   Both pre- and postnatal exposure

High exposure caused decreased
*physical endurance
*hand-eye coordination
*short-term recall and
*drawing ability

About half of the floriculture workforce is female. The women often work throughout pregnancy. In areas with intensive floriculture, many children are exposed to pesticides prenatally.
Most exposure is likely due to skin contact.

Mixed exposure mainly organophosphate, carbamate, and pyrethroide insecticides and dialkyldithiocarbamates and some other fungicides.
Cross-sectional study of children (N=166) attending 1st / 2nd grade of primary school (7-8 years old) in Tabacundo

Children, whose mothers had worked in floriculture during pregnancy had
- higher blood pressure
- reduced visuo-spatial function (lower drawing score in the Stanford-Binet Copying test)
- reduced motor function (finger tapping)


Prospective study of Danish children whose mothers worked in greenhouses during pregnancy

Funen
~ 200 commercial greenhouses producing mainly pot plants and flowers
~ 1000 employed, mostly women in fertile age groups

Compared to Ecuador:
Legal right to paid leave or replacement → shorter exposure
Long re-entry intervals for insecticides → lower exposure to neurotoxicants
Main exposure: fungicides and growth regulators
Hypothesis
• Occupational exposure to hormone disrupting pesticides in pregnancy may interfere with children's reproductive and neuro development and growth later in life.

Prospective study of Danish children whose mothers worked in greenhouses in early pregnancy

1st trimester enrollment 1997-2001
birth 2007-2008
3 months old 2011-2013
6-11 years N=314
11-16 years N=247
N=203
N=177
N=?
Exposure classification at enrollment

- Work functions
  Mainly re-entry activities
  Irrigating fungicides or growth regulators (17% of the women)
- Detailed information about the pesticides used in the working areas
- Exposed
  high
  medium
- Unexposed/low

Exposure occurred mainly within the first 8 weeks of pregnancy

~ 40% of the exposed women went on paid leave within the first two months of pregnancy

Others were replaced to pesticide-free areas
More than 100 different pesticides (active ingredients)

deltamethrin benomyl
carbaryl cypermethrin fenpropathrin iprodion penconazol amazin
carbofuran carbofuran bioremethrin dimethoat quinalphos mevinphos
deltamethrin paclotrazol
fenpropathrin methiocarb methyriamicarbe azinphos-methyl
fenvalerate methiocarb methomyl
deltamethrin cypermethrin carbofuran
methylmercaptometh aldicarb

Resbuthrin cyhalothrin fenvalerate

permethrin tau-fluvalinat

diflubenzuron esfenvalerate difethialon
propetamphos aldicarb
aldicarb carbaryl
phoxim malathion
heptenophos etrimfos
dimethoat dichlorvos
diazinon chlorpyrifos
azinphos-methyl acephat fenezaquin
fipronil dicofol
teflubenzuron kaliumoleat
imidacloprid abamectin
tetradifon rotenon
pyriproxyfen phosphin
methopren hexythiazox
lindan thiophanat

More than 100 different pesticides (active ingredients)

The most frequently used pesticides in the working areas (out of ~ 120 different)

<table>
<thead>
<tr>
<th>Insecticides</th>
<th>Fungicides</th>
<th>Growth regulators</th>
</tr>
</thead>
<tbody>
<tr>
<td>deltamethrin (PY)</td>
<td>captan</td>
<td>daminozid,</td>
</tr>
<tr>
<td>dichlorvos (OP)</td>
<td>chlorothalonil</td>
<td>paclobutrazol,</td>
</tr>
<tr>
<td>dimethoate (OP)</td>
<td>fenarimol</td>
<td>chloromequat,</td>
</tr>
<tr>
<td>chlorpyrifos (OP)</td>
<td>fosetyl-aluminium</td>
<td>chlorid,</td>
</tr>
<tr>
<td>endosulfan</td>
<td>iprodion</td>
<td>malathion</td>
</tr>
<tr>
<td>fenpropathrin (PY)</td>
<td>prochloraz</td>
<td></td>
</tr>
<tr>
<td>methiocarb (CB)</td>
<td>propamocarb</td>
<td></td>
</tr>
<tr>
<td>methomyl (CB)</td>
<td>tolclofos-methyl</td>
<td></td>
</tr>
<tr>
<td>pirimicarb (PY)</td>
<td>vinclozoin</td>
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</tbody>
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'Red' pesticides have endocrine disrupting properties in experimental studies

Shorter re-entry intervals for fungicides and growth regulators than for insecticides
• All the pesticides were approved for use in DK in accordance with EU legislation.

• All regulations for work environment including rules for use of pesticides were complied

• All safeguards and special measures to protect pregnant women were taken.

Findings in boys

Higher prevalence of cryptorchidism at 3 months

Exposed boys:
Reproductive hormones (inhibin B, FSH, LH and testosterone) affected

Reduced testis volume and penile length at 3 months and 6-11 years of age

Testicular volumes were lower in exposed boys at school age – and correlated to size at 3 months

\[ P=0.03 \text{ (adjusted for age and weight)} \]


Geo\text{}metric mean

Earlier breast development in exposed girls

OR=3.1, \( p=0.054 \)

Mean age (years) for onset of breast development

Exposed: 8.9 (8.2-9.7)

Unexposed: 10.4 (9.3-17.6)  
Earlier breast development in girls

Exposed girls compared to a reference group of Danish girls:
OR=3.4, p<0.0001

Aksølæde, L. et al, Pediatrics 2009

Lower birth weight in prenatally exposed children

Wohlfahrt-Veje et al. (2011) Environmental Health 10:79
Higher body fat percentage at school age in prenatally exposed children

Body fat percentage at school age was related to the prenatal exposure level

Adjusted for gender, age at examination, social class, and maternal smoking
Susceptibility gene

PON1 (paraoxonase)

- Detoxify organophosphate pesticides
- Antioxidant – protect against cardiovascular diseases
- A common genetic variant – a glutamine (Q)/arginine(R) substitution at position 192 affects both properties.

Prenatal pesticide exposure caused dose-related increase in body fat content and blood pressure at school-age in children with the PON1 192 R-allele

Outcomes were adjusted for gender, age at examination, social group, smoking in pregnancy and for blood pressure also BMI

Andersen et al. (2012), PlosOne, vol.7
Reduced neuropsychological functioning in girls after prenatal exposure to pesticides.

- Motor speech reduced – finger tapping
- Reaction time enhanced - CATSYS
- Language – lower scores
- WJ III Picture Vocabulary

No effect was evident for the boys.

Exposure level - assessment in humans

- Estimation from average food intake and residues measured
  - ‘You only see what you are looking for’
  - Variations in dietary habits
  - Relatively higher intake in children

- Biomarker – pesticides in urine or blood
  - Analytical methods/detection limits
  - Organophosphates most studied
Pesticide exposure in childhood

- For their body weight, children eat and breathe more than adults, thus a small exposure translates into a big dose.

- Behavior – hand to mouth increases exposure to chemicals

Urinary concentrations of organophosphate metabolites

Detectable in > 90% of the populations

Highest in children

Ref: Barr et al., Environ. Health Perspect., 2004 (112)
Urine concentration of two organophosphate metabolites in 23 children 3–11 years of age

chlorpyrifos

malathion

Exposure in pregnancy

Maternal urinary OP-metabolite concentration in pregnancy associated with:

- Reflex abnormalities in neonates < 2 months-of-age
- Delayed mental development at 24 months
- Attention deficits and increased ADHD score at 5 years
- Lower IQ at 7 years

CHAMACOS study (Eskenazi et al.)
Birth cohort study (N~380 children), in California Salinas Valley
Chlorpyrifos in pregnancy
Residential indoor use (USA) – until 2001

Concentrations in maternal blood associated with:
- reduced birth weight and length
- delayed mental and psychomotor development at 3 years of age
- lower IQ at 7 years

Birth Cohort Study in New York City, start 1998, N~300 (Rauh & Whyatt et al)

Correlations of surface measures with full-scale IQ in high- vs. low-CPF exposure groups.

Rauh V A et al. PNAS 2012;109:7871-7876
Conclusions

Occupational and/or residential pesticide exposure in pregnancy associated with:

- Impaired neurodevelopment in childhood
- Higher blood pressure at school age
- Impaired reproductive development
  - Reduced genital size and more malformations in boys
  - Earlier age of breast development in girls
- Effects on growth
  - Lower birth weight
  - Higher body fat content at school age

Conclusion

Exposure level

- From food - exact level unknown
  - random samples
  - not all pesticides included
- Mixed exposure
- Optimistic limits (MRLs)
  - developmental neurotoxicity and endocrine disrupting effects and mixture effects are not included
Are pesticide residues in food a health risk to the population?

We do not know, but

- Risk depend not only on dose but also on developmental stage at time of exposure
- Exposure during development may cause a wide range of effects and may increase the risk of dysfunction and/or disease later in life
- Pregnant women and children and genetically susceptible individuals may not be adequately protected