Links between in utero exposure to pesticides and effects on the human progeny
Does European pesticide legislation protect health?

AREHNA workshop
« Environmental impact on congenital diseases »
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Catherine Wattiez, Dr.Sc.
Pesticides Action Network (PAN) Europe
Sources of information

1) Systematic review of pesticide human health effects, 2004, Ontario College of Family Physicians


3) In Harm’s way: toxic threats to child development, 2000, Greater Boston Physicians for Social Responsibility
Contamination pathways

Mothers can be exposed

Directly through:
- food, water and other drinks
- occupational use
- gardening, household use including by professional applicators
- the house being located near sprayed field or in intensive pesticide use area
- Moreover, since female ova formed at fetal stage and environmental contaminants have been found in follicular fluid, the next generation of children born may be affected by their grandmother’s exposure.

Indirectly through:
- partner’s professional or amateur use (pesticides and dust with pesticides brought back at home on clothing, vehicles, …)
Any Birth defects

1) **Garcia AM et al, 1998, Spain**, exposure evaluated for farmer parents 1-3 month prior conception and during the first trimester of pregnancy: for all defects, significant association with pyridil derivatives exposure

2) **Rojas A et al, 2000, Chile**: various congenital malformations associated with mother and father agricultural work or house located within the spraying area.

3) **Nurminen T et al, 1995, Finland**, 5 levels of exposure: significant association between exposure in the first trimester of pregnancy through agricultural work and all birth defects (pooled)

4) **Crisostomo L et al, 2002, Philippines**, household exposure or through conventional farming or IPM farming 3 months before and during first trimester of pregnancy: conventional pesticide users 4 times more at risk than IPM users

5) **Garry VF et al, 1996, USA Minnesota**: birth defects linked with parents being pesticide applicators or in the general population of heavily agricultural regions. Most significant association with 2,4-D and various fungicides
Central nervous system defects

1) **Shaw GM et al., 1999, USA**: occupational and household exposure 1 month before and 3 after conception neural tube defects (mother gardening or living within 0, 25 miles of an agricultural crop)

2) **Kristensen P et al., 1997, Norway**: spina bifida and hydrocephaly associated with farmer parents

3) **Rojas A et al., 2000, Chile**: CNS defects linked with farmer parents and house location close to the spraying area
Cardiovascular defects

1) **Loffredo CA et al, 2001, USA**, 4 exposure groups 3 months before and 3 after conception: cases of transposition of the great arteries associated with maternal exposure during the first trimester of pregnancy.

2) **Shaw GM et al, 1999, USA**, occupational and household exposure 1 month before and 3 after conception: cases of conotruncal defects associated with use of pesticides for gardening by mother.

3) **Correa A et al, 1991, USA**, total anomalous pulmonary venous return associated with occupational and household exposure to pesticides.
Oral cleft

1) Nurminen T et al, 1995, Finland. 5 levels of exposure: cases of orofacial cleft associated with agricultural work

2) Shaw GM et al, 1999, USA. occupational and household exposure 1 month before and 3 after conception: cases of multiple cleft lip with/without cleft palate, associated with paternal exposure

3) Gordon JE et al, 1981, USA: doubling of risk with occupational exposure during the first trimester of pregnancy
Eye anomalies

Dimich-Ward H et al, 1996, Canada, births from father saw mill workers (exposed to chlorophenate up to 3 months prior to conception or in the 3 months or through the entire period of pregnancy):

**Results:** strongest association with father exposed in the 3 months prior to conception but significant when exposed through the entire period of pregnancy
Urogenital defects

1) Garcia-Rodriguez J et al, 1996, Spain. provinces categorized in 4 exposure levels: cases of orchidoplexy associated with the 3 highest levels of exposure and increase of risk positively correlated with exposure level.

2) Kristensen P et al, 1997, Norway. exposure deduced from amount of money spend on the farm + on tractor equipment: parents exposure associated with cryptorchidism and hypospadias.

3) Weidner IS et al, 1998, Denmark. cases of hypospadias associated with parents farming and gardening exposure during the year of conception, cryptorchidism associated with gardening only.
Limb defects

1) **Engel LS et al, 2000, USA**: link with maternal agricultural work

2) **Kristensen P et al, 1997, Norway**: link with farmer parents

3) **Shaw GM et al, 1999, USA**: exposure 1 month before and 3 months after conception: association with use of pesticides products for gardening by mothers and with professional application of pesticides in their home

4) **3 other references selected in the 2000 report of Physicians for Social Responsibility**: link with garden, workplace and household parental exposure
Intrauterine growth retardation (IUGR)

Associated not only with poor neonatal health but with chronic problems later in life (hypertension, type 2 diabetes, breast and prostate cancer)

The Ontario College of Family Physicians report cites 7 studies showing a positive association between pesticide parental exposure and IUGR:
- one is focusing on the association with pyrethroids exposure
- another is focusing on the association with chlorpyrifos exposure

The Physicians for Social Responsibility report cites 2 additional studies:
- Munger RG et al, 1997, USA (Iowa): association with women exposure to drinking water contaminated with various herbicides including atrazine, cyanazine and metolachlor
- Karmans H et al, 1995, USA: association with women exposed to PCDFs, pentachlorophenol and lindane
Neurodevelopmental impairments (1)

Include mental retardation, dyslexia, Attention Deficit Hyperactivity Disorders (ADHD), learning deficit, memory losses, aggressive behaviour, autism and autism like disorders

Incidence of developmental disabilities is increasing in USA. But what about Europe?

Rodents studies often vastly underestimate the sensitivity of the developing brain (2-4 orders of magnitude)

The brain is known to be subject to environmental influences at all phases of development, with critical
Neurodevelopmental impairments (2)

ANIMAL TESTS

Organophosphates:
N.B. Neurotoxicity regulatory tests are not designed to measure effects of OP on cell proliferation and differentiation despite recent evidence (PSR) that acetylcholinesterase may play a direct role in neuronal differentiation

1) **Single dose of an OP (DFP)** to mice on postnatal day 10 causes hyperactivity at 4 months of age

2) **Chlorpyrifos** causes neurochemical and behavioural effects in rats exposed during gestation up to the second generation as well as when exposed neonatally. It decreases DNA synthesis in the developing brain resulting in deficit in cell numbers at concentrations lower than some indoor exposure levels
**Neurodevelopmental impairments (3)**

**ANIMAL TESTS**

**Organochlorines**

1) Prenatal rats exposure to dieldrin induced permanent behavioral alterations in adulthood

2) Newborn mice given a single dose of DDT at day 3, 10 or 19 show a permanent increase in activity level only when exposed at day 10, highlighting a short but significant window of vulnerability
Neurodevelopmental impairments (4)

ANIMAL TESTS

Pyrethroids

1) Mice given bioallethrin or deltamethrin on day 10 of life result in hyperactivity as adults. The dose /response is a U curve likely to have not been identified by current regulatory testing methods.

2) Fenvalerate and cypermethrin gestational and lactational exposures show alterations in levels of neurotransmitter enzymes. Neuroreceptors levels were also permanently altered and hence behaviour.
Neurodevelopmental impairments (5)

HUMAN STUDIES

1) **Guillette EA et al, 2000, Mexico:** children exposed in utero (biomonitoring data) to a variety of organochlorine pesticides in agricultural community in Mexico show impaired stamina, coordination, memory and capacity to represent familiar subjects in drawing.

2) **Garry VF et al, 2002, USA:** increased risks of neurobehavioral disorders in children associated with parental occupational use of glyphosate
Does European pesticide policy protect our health? (1)

1) The European Environment and Health Action Plan

Leaves pesticides environment and health risk reduction initiatives to the pesticides autorisation Directives (PPP + biocides) and to the future Thematic Strategy on the Sustainable Use of Pesticides according the EP Resolution Feb 05:
- is at best a research action plan
- fails to consider:
  * the precautionary principle
  * risks for foetuses, infants and children
  * immediate exposure reduction actions
Does European pesticide policy protect our health? (2)

2) The PPP authorisation directive 91/414/EEC

Risk assessment = basis for inclusion on a positive list of active substances accepted at EU level, but risk assessment not properly evaluated as improper evaluation of both toxicity and exposure.

In the existing Directive:
- no specific test required for identification of EDCs properties
- no systematic testing to identify immunotoxic or neurotoxic properties
  (except for OP or OP like neurotoxicants)
- no sufficiently specific developmental neurotoxicity / immunotoxicity / endocrine / reproductive toxicity tests required
- no consideration for possible combined effects
- formulated product only subject to very few tests; « inert » ingredients not tested
- no systematic review of the scientific litterature required
Does European pesticide policy protect our health? (3)

In the Commission draft modifications proposal

1) positive list for safeners and synergists and negative list for co-formulants but still very few tests on the formulated product

2) too weak exclusion criteria for active substance EU acceptance:

   * M (I) or M(II) unless threshold dose is estimated safe for humans [no I, no II presently on the market]
   * C(I) or C(II) unless threshold dose estimated safe [no I, no II presently on the market]
   * R (I) unless exposure to humans is unlikely [only 1 I presently on the market]

   No consideration for EDCs properties or neuro / immuno / endocrine / other reproductive developmental toxicities
Does European pesticide policy protect our health? (3)

3) too weak criteria for definition of active substances of concern candidate for substitution:
   * only if classified as dangerous (according to Directive on classification p and l of dangerous substances 67/548/EEC) \textit{and} present in the PPP at concentrations leading the product to be dangerous according to Directive on classification, p and l of dangerous preparations (1999/45/EC) [CMR, sensitizing subst.]

\textit{No consideration for EDCs, neurotoxic, immunotoxic properties or neuro / immuno / endocrine / other reproductive developmental toxicities}

4) New testing requirements in annexes discussed behind closed doors: \textit{what about specific tests for identification of EDCs, systematic tests on neurotoxic and immunotoxic potential, sufficiently specific developmental neurotoxicity / immunotoxicity / endocrine / other reproductive toxicity tests?}

5) Extensive review of the scientific literature still not required

6) Pesticides have to be used according to « proper use » but IPM not required
Does European pesticide policy protect our health? (4)

3) The future Thematic Strategy on the Sustainable Use of Pesticides

Some measures forecasted aimed at risk reduction but:

* only by reduction of the use of « unintended pesticides »

* no precautionary dependency/use reduction measures (no link seen between dependency and risk reduction)

* no targets and timetables for risk reduction
Does European pesticide policy protect our health? (5)

* shortage of incentives for farmers to convert towards IPM or ICM
  - IPM definition is the one of industry (aimed at pesticides optimisation but not at pesticide dependency reduction)
  - ICM to be defined later as a result of MS data collection of PPP use per crop type

* no further incentives for farmers to convert to organic farming

* no pesticide tax forecasted to finance reduction measures

* no ban of aerial spraying (concept of « proper aerial spraying »)
Agenda for pesticides policy changes

**September 2005:**
- Commission proposal PPP autorisation Regulation
- Commission proposal TS sustainable use of pesticides

**1st half of 2006:** European Parliament opinion

**2d half of 2006:** Council opinion (Finnish Presidency)