



# The impact of pesticides on fetus and children: Their special vulnerability to neurotoxic and endocrine disrupting pesticides



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# ROUTES OF EXPOSURE TO PESTICIDES

- Ingestion
- Inhalation
- Dermal absorption
- Transplacental
- Breast milk
- SPECIAL EXPOSURE  
IN RURAL AREAS



WHO



# Potential risk from exposure preconception and in utero

Pesticide exposure to either mother or father before conception, or to mother during pregnancy, has been associated with increased risk of

- foetal death,
- spontaneous abortion and
- early childhood cancer.



- There is increasing evidence of in utero exposure and increased risk of

**growth retardation.**

congenital anomalies hypospadias, cryptorchidism defects,

central nervous system and Heart defects.



# Neurodevelopmental behavioural intellectual disorders

## The silence pandemic

1 in 6 -10 children in USA and Europe suffer from  
developmental disabilities

- Cerebral Palsy

➔ IQ

➔ Learning disabilities

- developmental  
delays,

➔ Behavioural problems

➔ sensory deficit,

➔ Attention Deficit

Hyperactivity Disorder  
(ADHD)

➔ Autism



# CHILDREN ARE NOT LITTLE ADULTS. WHY????

● EXPOSURE

● SUSCEPTIBILITY

● UNDER PROGRAMMING AND DEVELOPMENT

# Exposure:

## HIGHER AND UNIQUE

- Higher need of energy, water, oxygen/per BW, larger surface /BW
- Higher distribution and absorption including dermal one



# UNIQUE SUSCEPTIBILITY

1. Immature Immune System - Reduced Bio transformation, and Elimination
2. Less ability to Detoxify & Excrete
  - ✓ The newborn child has low levels of the enzyme paraoxanase-1, which detoxifies organophosphate pesticides including chropyriphos
  - ✓ In fetal periods and the first 6-12 months the P450 cytochrome systems and glutathione conjugation are significantly reduced in efficiency, this may increase the duration and amount of any given internal dose
3. The blood-brain barrier is not fully developed for the first 36 months of life so neurotoxicants readily cross into the CNS

Ref. Philip J. Landrigan, et al EHP v107 Supp 3 jun 99



# PROGRAMING AND DEVELOPING

Children are growing and developing, and their delicate developmental processes are easily disrupted. **Toxic factors may operate to harm child by mechanisms that do not operate in the adult<sup>1</sup>**

If cells in an infant's brain are destroyed by pesticides,  
if reproductive development is diverted by EDCs  
if development of the immune system is altered,  
the resulting dysfunction can be permanent and irreversible

1. Ref. Philip J. Landrigan, et al EHP v107 Supp 3 jun 99

- Foetus and Child Development is **UNIQUE** as it is susceptible at critical windows of their growth .....(WHO 2005).
- These critical windows of vulnerability **have no parallel in adult physiology and create unique risks** for children exposed to hazards which can alter normal function and structure



# WINDOWS OF SUSCEPTIBILITY

# THE TIMING OF THE EXPOSURE

# WINDOWS OF VULNERABILITY

INTERVENATION on PROGRAMMING  
AND DEVELOPMENT IN PARTICULAR OF  
FOETUS AND CHILD

faster cell division  
More susceptible  
to genotoxic effects

WEAKENING The DEFENSE



# Essential Processes during development can be disrupted/diverted

- **LATENT effects:** triggered by early **exposures** and may not be detected until much later in life.
- **Effects during development may be manifested as:**
  - persistent deficits,
  - developmental delays, or transient deficits
  - **May also be epigenetic in nature**

**Latent effects**

Ref Deborah Rice<sup>1</sup> and Stan Barone Jr.<sup>2</sup>Abstract,

\* WHO 2011 modules



# Human Body communication/cell signalling system

Endocrine system

- ❖ "Hormones" - includes also neuro-hormones, and intercellular and intracellular chemical regulators (cytokines and intracrine),
- ❖ can act at levels ppt-ppb
- ❖ Can be affected by EDCs

Body communication system

Nervous system

Immune system



# Adults Vs Child: Differences in Cell Signalling & Communication System

- The foetus relies almost exclusively on the cell signalling systems to control cellular proliferation and migration
- Endocrine/ cell signalling interrupting and neuro toxicants can affect the reproductive, the immune &, nervous system.the whole development of fetus and child till adolescence
- Adults in contrast to children have well developed homeostasis
  - negative feedback and buffering systems to control and protect the cell signalling-system



# The THYROID FUNCTION

- Exposure of pregnant women and infants: thyroid disruption may have deleterious effects on neurological outcome
- Persistent OCL, OPS, Carbamates, Pyrethroids can affect thyroid function
- Minor alterations in thyroid homeostasis may have **permanent effects during sensitive windows of brain development** (foetal life and infancy up to 2y )
- Auso et al., 2004; Lavado-Autricet al., 2003; Nicholson and Altman, 1972)
- Berbelet al., 2009; Pop et al., 2003; Sala et al., 2001.
- Boas, M., et al. Thyroid effects of endocrine disrupting chemicals. *Molecular and Cellular Endocrinology* (2011),doi:10.1016/j.mce.2011.09.005



- EDCs: There are **HIGH RISKS** as well as scientific **Controversies** (low dose, extrapolation, threshold, mixtures)



# KEY CHARACTERISTICS OF ENDOCRINE DISRUPTION

- Strongly depend on the Age
- There is Latency from exposure
- Transgenerational, epigenetic effects linked to EDCs
- Importance of mixtures in increasing risks
- Non traditional dose-response dynamics
- Bioactive at extremely low doses

e.g ppt



MN Brune

Ref.

- WHO Modules 2011 on EDD
- Diamanti-Kandarakis, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *The Endocrine Society*. 2009



# *Low Exposures at ppb or ppt??*



# EDSs Large effects from small exposures.

Extrapolation???

- the low-dose ranges of biological activity can be predicted from the hormonal action mechanisms and the physiology of delivery of EDCs
- Toxicology assumes that it is valid to extrapolate linearly from high doses over a very wide dose range to predict responses at extremely low doses

■ **BUT IS THIS Assumption Valid ??**

*Ref. Environmental Health Perspectives; 6/15/2003; vom Saal, Frederick S.,*



# EDCs Large effects from small exposures. The example of estrogenic EDCs

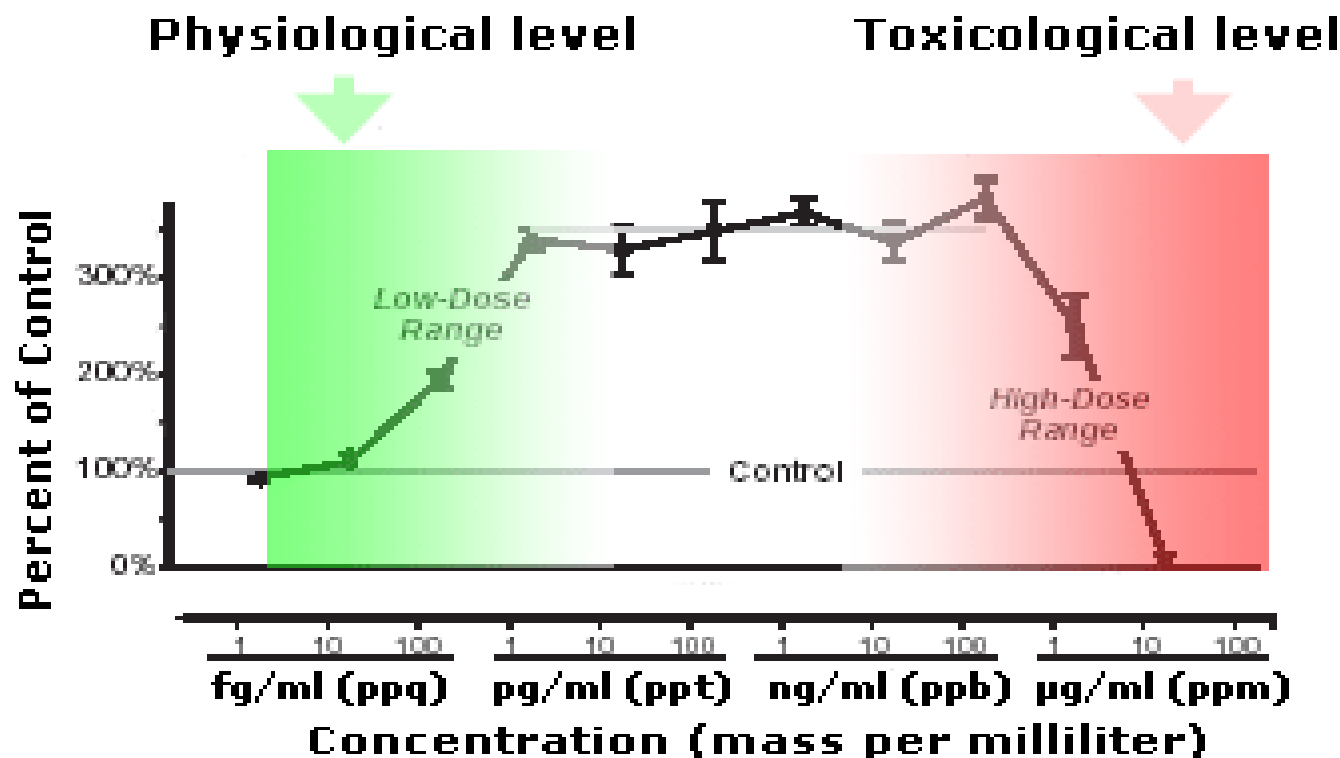
**EXTRAPOLATION???**

- The receptor-mediated responses can first increase and then decrease as dose increases, Because the receptor-mediated responses can saturate, linear extrapolation from high doses across a wide dose range, to predict responses at doses within the physiological range of receptor occupancy, is invalid.
- 
-

# The dose response monotonic curve is not followed

(graphed from Welshons *et al.* 2003)

Extrapolation?



**Fig 1: The proliferation response of MCF-7 cells to estradiol over exposure 1, Response is displayed as a percent of the proliferation seen in the control group (Figure adapted from Welshons)**



# BRAIN DEVELOPMENT

The interaction of genetic inheritance and environment determines how the brain will develop.

- Brain development is more vulnerable on early exposures
- 80% of the brain as organ develops by 4y
- During the first 3-4y the development of intelligence, personality and social behaviour occurs more rapidly: approximately half of the intellectual development potential is established by the age of 4



Toxic substances (neuro and EDCs) and factors can drain the brain and compromise inherent and other kai physiological potentials. The effects can appear later Serious Latent neurotoxicity can be a consequence of exposure during development even to low



Latent effects

From Ph. Grandjean  
on **Chemical Brain Drain**, 2014

SCMichaelidou

Exposure during brain growth may exert subtle, permanent effects on the structure and function of the brain. These include:

- neuronal and axonal differentiation;
- alteration of serotonergic system
- altered myelination and synaptogenesis and programming of synaptic function.

*Ref:* Slotkin. Guidelines for developmental neurotoxicity and their impact on organophosphate pesticides: a personal view from an academic perspective, *Neurotoxicology*, 2004, 25:631.



# Effects on IQ from a Prenatal exposure to OPS (ref Lanphear 2014)



- **Exposure of Pregnant women to OPS** has been associated with a 5-point drop in IQ of the baby when maternal blood levels rise from 10 to 75 parts per billion (ppb).

# Association of pyrethroid pesticide exposure with attention-deficit/hyperactivity disorder in a nationally representative sample of U.S. children.

Schuman Wagner Melissa et.al Environ Health. 2015; 14: 44. Published online

Pyrethroid pesticides is known to cause abnormalities in the **dopamine system** and produce an ADHD phenotype in animal models

1. A national representative sample of 687 children aged 8-15y in the USA was used, urinary levels of pyrethroid metabolite was followed and ADHD symptoms assessed. ,
2. .A correlation between increasing exposure to Pyrethroids (metabolite 3-phenoxybenzoic acid (3-PBA)) and the **ADHD (Attention Deficit hyperactivity Disorder)** was found , which may be stronger
  - ➡ for hyperactive-impulsive symptoms compared to inattention
  - ➡ in boys compared to girls.

## Neurodevelopmental Disorders and Prenatal Residential Proximity to Agricultural Pesticides: The CHARGE Study

Janie F. Shelton,<sup>1</sup> Estella M. Geraghty,<sup>2</sup> Daniel J. Tancredi,<sup>2,4</sup> Lora D. Delwiche,<sup>1</sup> Rebecca J. Schmidt,<sup>1</sup> Beate Ritz,<sup>5,6,7</sup> Robin L. Hansen,<sup>2,8</sup> and Irva Hertz-Picciotto<sup>1,9</sup>

**Distance from application 1.25, 1.50, 1.75 km**

Positive correlations were found between prenatal exposure to OPS and autism as well as correlation with exposure to pyrethroids 3 months before conception.

Less strong correlations were found for Developmental Delays


Children may be at increase risk of neurodevelopmental disorders when their mothers during pregnancy are exposed to OPS, carbamates or pyrethroids.



# The PROBLEM OF MIXTURES

EU Monitoring of Pesticides Residues 2013 (Ref EFSA 2015)

- MULTIPLE RESIDUES in 27.3 % of the samples (22 126)
- Coordinated Monitoring: More than 1 found in all food products
  - Strawberries in 63%
  - Peaches in 53%
  - Apples in 46%
  - Lettuce in 36%
  - Milk 3.5%



**COMBINED  
TOXIC  
EFFECTS**



# Limitations of current Regulatory Toxicology & Risk Assessment

1. Only one chemical is considered at a time: It is critical to move **beyond the piecemeal, one chemical at a time, one disease at a time, one dose approach**
2. The underlying mechanism of complex interactions of chemicals or chemicals with environment and gene factors, is still a **BLACK BOX**
3. Inadequate information on what is children's overall and combined exposure from many routes and many chemicals.
4. It is still Predicated on adult toxicology and does not always account for the unique exposure and special vulnerability of foetus and children and that development can be "hijacked" at even low (safe) dose of many chemicals acting together

based on "Applying the precautionary principle in environmental risk assessment to children", EUR/04/5046267/BD/9, Ph.J. Landrigan & L. Trasande



# Limitations of current Regulatory Toxicology & Risk Assessment

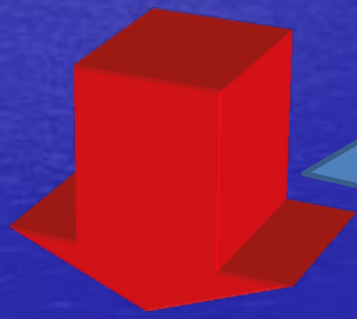
5. In particular for the evaluation of EDCs controversies and high degree of uncertainty of the science behind EDCs (non monotonic dose response, threshold , multiple effects/exposures) . Missing criteria for classification.
6. There is lack of standardized tests to cover:
  - ❖ all potential effects beyond oestrogen, androgen, thyroid, or steroidogenesis (EATS) or disease syndrom or multiple disease ,
  - ❖ mammalian test to cover effects on vulnerable stages of early life (foetal) or pubertal which may emerge during later life stages ,may not exist (Efsa SC 2013)
- ❖ Synergistic effects of many EDs co-acting at low concentration ???



# RISK MANAGEMENT WITHIN THE UNCERTAINTIES

## Precautionary Principle COM 2000

UNCERTAINTIES  
MAY ACT As  
DECENTIVE to ACT



THE  
CHALLENGE  
Rational  
application

# Inclusive Risk Governance

# APPLICATION of the Precautionary Principle within an Inclusive Risk Governance

## RISK MANAGERS :

- Need to be supported for a rational-balance and to be able to extend possible application of **SCIENCE BASED PRECAUTIONARY PRINCIPLE**
- Need to judge
  - different scenarios and
  - uncertainties against **potential risks of inaction.**

**RISK ASSESSORS & Scientists PROVIDE risk managers support based on the best available & emerging science**

**HOW?**

# APPLICATION of the Precautionary Principle within an Inclusive Risk Governance

## RISK ASSESSORS & Scientists

- Should be well aware of children's Vulnerability
- Consider state of the art /emerging science and data in balance with standardised data.
- **Clear expression of uncertainty;** explicit disclosure of hypotheses used and rational of decision reached in the absence of supporting or convincing evidence , Visualise both potentials a limitations of their methods and data
- **Gaps in data:** How this can potentially impact a specific Assessment and its robustness
- Gaps in children relevant data should be specifically mentioned and addressed with caution
- Provide alternative scenarios to RM

RISK MANAGERS





# FINAL MESSAGES

- Infants and children are not Little Adults. They have Key windows of vulnerability during critical stages in their development.
- **Pesticides is essential well regulated component of chemical risks**
- **But Uncertainties ignorance and scientific controversies still exist. These should not let to inaction**
  - They have to be minimized if possible (dynamic nature) (the role of research) and in the mean time
  - They have to be dealt with by applying precaution through an holistic intervention at all levels SOCIETY-SCIENCE-REGULATION
  - **Additional Safety factors should be applied when evidence for pre- and postnatal toxicity does exist or toxicity data applicable for children are lacking**



# FINAL MESSAGES

- RISK Assessment is well developed and a robust approach to be applied for all chemicals, **provided** that it can be supported with appropriate data and state of the art methodology to cover all diverse end points, potential effects and vulnerable groups.
- If not or when the degree of open scientific questions and uncertainties is still high, **hazard based and precautionary management approaches should be applied (as interim situation) leading to minimization of exposure to Pesticides of concern.**
- **CHILDREN ARE THE FUTURE OF OUR PLANET ..and their protection is our collective Responsibility**



# THANKS FOR YOUR KIND ATTENTION

CYPRUS NATIONAL COMMITTEE  
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