Workshop EFSA-ANSES

« Use of Epidemiological findings in Regulatory Pesticide Risk Assessment »

André Cicolella

Réseau Environnement Santé

February 18, 2015 Paris

Methodological problems

- **Study selection : 2006 -2012 ?**
- **Judgment Criteria : cf Inserm ++ / +/ +- ; Sanborn : Score**

- Definition of Criteria for classification
- Analysis by subgroups (genetic , type of exposure : chlordecone in Martinique …) vs metanalyses
- Comparison with other reviews : discrepancy analysis

- Window of sensibility for Endocrine disruptors➔ New design

Familles et substances actives impliquées dans les excès de risque du cancer de la prostate

Familles Substances actives	Populations concernées par un excès de risque significatif	Présomption d'un lien
Organochlorés		
Chlordécone	Population générale	++
Dieldrine	Population générale	±
β HCH	Population générale	±
Chlordane (trans nona-chlore)	Population générale	±
Organosphorés		
Coumaphos	Agriculteurs avec antécédents familiaux de cancer de la prostate	+
Fonofos	Agriculteurs avec antécédents familiaux de cancer de la prostate	+
Carbamates/thiocarbamates/dithiocarbamates		
Butylate	Agriculteurs	+
Carbofuran	Agriculteurs avec antécédents familiaux de cancer de la prostate	+
Pyréthrinoïdes		
Perméthrine	Agriculteurs avec antécédents familiaux de cancer de la prostate	+

Inserm

Non-cancer health effects of **pesticides**: systematic review and implications for family doctors. **Sanborn** M, Kerr KJ, Sanin LH, Cole DC, Bassil KL, Vakil C. Can Fam Physician. 2007 Oct;53(10):1712-20. Review.

1992-2003

Table 1. Summary of studies reviewed

HEALTH EFFECT	NO. OF STUDIES FOUND	NO. OF STUDIES INCLUDED*	SUMMARY OF RESULTS	MEAN GLOBAL SCORE OF STUDIES INCLUDED*
Dermatologic effects	11	10	7/10 studies positive for dermatitis with pesticide exposure	4.50
Neurotoxicity	60	41	39/41 studies positive for increase in 1 or more neurologic abnormalities with pesticide exposure	4.99
Reproductive outcomes	64	59	Birth defects: 14/15 studies positive; time to pregnancy: 5/8 studies positive; fertility: 7/14 studies positive; altered growth: 7/10 studies positive; fetal death: 9/11 studies positive; other outcomes: 6/6 studies positive	4.83
Genotoxicity	15	14	11/14 studies positive for increased chromosome aberrations with pesticide exposure†	5.03

*Assessors scored each paper on a 7-point scale for methodologic quality from 1—very poor to 7—excellent. Papers scoring <4 were excluded.
†Figure 1 aggregates results from all 14 genotoxicity studies.

Methodological problems

- Study selection : 2006 -2012 ?
- Judgment Criteria : cf Inserm ++ / +/ +- ; Sanborn : Score

- **Definition of Criteria for classification**
- **Analysis by subgroups (genetic , type of exposure : chlordecone in Martinique …) vs metanalyses**
- **Comparison with other reviews : discrepancy analysis**

- Window of sensibility for Endocrine disruptors➔ New design

Inserm

Présomption d'un lien entre exposition aux pesticides et cancer de la prostate

Exposition	Populations concernées par un excès de risque significatif	Présomption d'un lien
Pesticides (sans distinction)	Agriculteurs, applicateurs, ouvriers en industrie de production	++

++ d'après les résultats de 6 méta-analyses et une étude de cohorte (AHS) prospective

La cohorte prospective *Agricultural Health Study* (AHS) aux États-Unis, menée auprès d'exploitants agricoles et d'applicateurs de pesticides, a confirmé le risque accru de survenue de cancer de la prostate chez les exploitants agricoles applicateurs de pesticides (de l'ordre de 19 %) ainsi que chez les applicateurs professionnels de pesticides (de l'ordre de 28 %).

EFSA : "Overall, there is no evidence supporting an association between pesticide exposure and prostate cancer. "

Familles et substances actives impliquées dans les excès de risque du cancer de la prostate

Familles Substances actives	Populations concernées par un excès de risque significatif	Présomption d'un lien
Organochlorés		
Chlordécone	Population générale	++
Dieldrine	Population générale	±
β HCH	Population générale	±
Chlordane (trans nona-chlore)	Population générale	±
Organosphorés		
Coumaphos	Agriculteurs avec antécédents familiaux de cancer de la prostate	+
Fonofos	Agriculteurs avec antécédents familiaux de cancer de la prostate	+
Carbamates/thiocarbamates/dithiocarbamates		
Butylate	Agriculteurs	+
Carbofuran	Agriculteurs avec antécédents familiaux de cancer de la prostate	+
Pyréthrinoïdes		
Perméthrine	Agriculteurs avec antécédents familiaux de cancer de la prostate	+

Inserm

Can Fam Physician. 2007 Oct;53(10):1704-11.**Cancer health effects of pesticides: systematic review.** Bassil KL[1], Vakil C, Sanborn M, Cole DC, Kaur JS, Kerr KJ.

1992-2003

Cancer health effects of pesticides | Research

Table 1. Global quality score of studies included: *Studies are organized by type of cancer; 104 studies were found, and 83 were included.*

TYPE OF CANCER	NO. OF STUDIES FOUND	NO. OF STUDIES INCLUDED	SUMMARY OF RESULTS	AVERAGE GLOBAL QUALITY SCORE OF STUDIES INCLUDED
Lung	4	4	2/4 found positive associations	4.1
Breast	12	6	5/6 found positive associations; 1 found decreased risk with exposure	5.0
Pancreatic	3	3	All found positive associations	4.7
Non-Hodgkin lymphoma	32	27	23/27 found positive associations	4.5
Leukemia	23	16	14/16 found positive associations	4.5
Brain	11	11	All found positive associations	4.7
Prostate	10	8	All found positive associations	4.8
Stomach	1	1	Found a positive association	5.0
Ovarian	1	1	Failed to find an association	5.5
Kidney	7	6	All found positive associations	4.2

EFSA : "Overall, there is no evidence supporting an association between pesticide exposure and prostate cancer. "

réseau ENVIRONNEMENT SANTÉ RES

Int Arch Occup Environ Health. 2004 Nov;77(8):559-70. Epub 2004 Nov 18.

Prostate cancer among pesticide applicators: a meta-analysis.

Van Maele-Fabry G[1], Willems JL.

RESULTS:

The meta-rate ratio, based on 22 estimates of RR, is 1.24 [95% confidence interval (95% CI) 1.06-1.45]. This pooled risk estimate for the occupational categories selected is higher than the one previously calculated for farmers in general over a shorter period of publication. Substantial heterogeneity of rate ratios exists between the different studies. The major source of heterogeneity identified is geographic location. Increased meta-rate ratios are observed for studies derived from North America as well as from Europe, the meta-rate ratios from Europe being lower than those from North America. There is no obvious indication of publication bias.

EFSA : "Overall, there is no evidence supporting an association between pesticide exposure and prostate cancer. "

Occup Environ Med. 2003 Sep;60(9):634-42.

Occupation related pesticide exposure and cancer of the prostate: a meta-analysis.

Van Maele-Fabry G[1], Willems JL.

RESULTS:

The meta-rate ratio estimate, based on 25 estimators of relative risk from 22 studies, was **1.13 (95% CI 1.04 to 1.22).** Significant heterogeneity of rate ratios existed among the different studies. Therefore, a stratified analysis was carried out. Major sources of heterogeneity identified were geographic location, study design, and healthy worker effect. Overall, pooled risk estimates for studies derived from Europe were lower than those derived from the USA/Canada. A significant increase in rate ratio was observed for the occupation category of pesticide applicators, whereas no significant increase was observed for farmers. There was no evidence of publication bias.

EFSA : "Overall, there is no evidence supporting an association between pesticide exposure and prostate cancer. "

J Clin Oncol. 2010 Jul 20;28(21):3457-62. doi: 10.1200/JCO.2009.27.2153. Epub 2010 Jun 21. **Chlordecone exposure and risk of prostate cancer.** Multigner L[1], Ndong JR, Giusti A, Romana M, Delacroix-Maillard H, Cordier S, Jégou B, Thome JP, Blanchet P.

RESULTS:

We found a significant increase in the risk of prostate cancer with increasing plasma chlordecone concentration (odds ratio [**OR], 1.77; 95% CI, 1.21 to 2.58** for the highest tertile of values above the limit of detection [LD]; P trend = .002) and for cumulative exposure index **(OR, 1.73; 95% CI, 1.04 to 2.88** for the highest quartile; P trend = .004). Stronger associations were observed among those with a positive family history of prostate cancer and among those who had lived in a Western country. The rs3829125 and rs17134592 allele variants were in complete linkage disequilibrium and were found at low frequency (0.04). Among subjects with plasma chlordecone concentrations above the LD, **carriers of the allele variants had a higher risk of prostate cancer (OR, 5.23; 95% CI, 0.82 to 33.32).**

CONCLUSION:

These findings support the hypothesis that exposure to environmental estrogens increases the risk of prostate cancer.

EFSA : "Overall, there is no evidence supporting an association between pesticide exposure and prostate cancer. "

Methodological problems

- Study selection : 2006 -2012 ?
- Judgment Criteria : cf Inserm ++ / +/ +- ; Sanborn : Score

- Definition of Criteria for classification: ??
- Analysis by subgroups (genetic , type of exposure : chlordecone in Martinique …) vs metanalysis
- Comparison with other reviews : discrepancy analysis

- **Window of sensibility for Endocrine disruptors➔ New design**

Risk assessment ? ➔ Communication ?

- Epidemiology is not the only way to analyse risk
  - Past exposure
  - Insufficient knowledge on chemicals and timing of exposure
- From a precautionnary point of view, toxicological data must be considered first ; toxicological studies must be designed by using low doses, exposure time from pregnancy to whole life.