UNIVERSITÉ CAEN NORMANDIE

Centre Baclesse unicancer NORMANDIE - CAEN

Anticipe INSERM U1086

Inserm Institut national de la santé et de la recherche médicale

EPICENE / Cancers et expositions environnementales INSERM U1219

Joint EFSA-BfR International Conference on Using Epidemiological Studies in Health Risk Assessments: relevance, reliability and causality

Epidemiological results on pesticides and cancer, just a matter of p values and confounding?

AGRICAN AGRICULTURE & CANCER

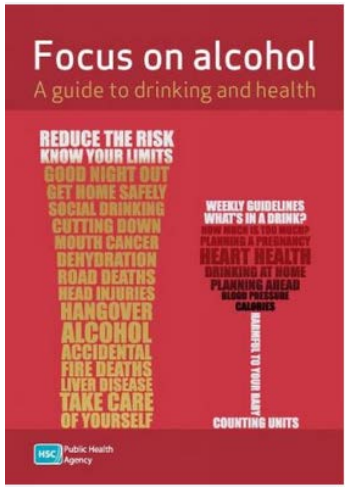
https://www.agrican.fr/

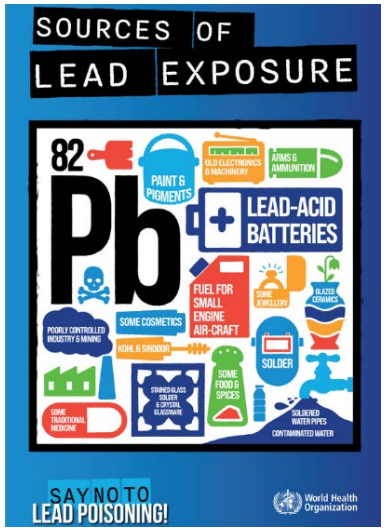
Pierre Lebailly & Isabelle BALDI

Epidemiology = key science for public health & populations

Calculating increases in risk in relation with exposures/behaviours….

…To determine **preventive actions** : informing Public Health decision makers





At the **heart of social debates**:

- **simple messages** to be understood by everyone
- **complex methods and concepts not understandable by everyone…**
  - *Covid: 60 millions of epidemiologists in France!*

Epidemiological complexity: various study designs

- **What the non epidemiologists think and say**
  - *Cohorts > Case-control > cross-sectional studies*
- **What epidemiologists know:**
  - All designs are valuable and useful
  - Depends on the research question, frequency of exposure and disease

Complete understanding and conclusions
= **combination of studies**, with different designs, in different populations

Collective expertise or reviews on a range of studies with various methods
Not only **meta-analysis** but also individual studies (more informative)

Epidemiological complexity: various study designs Consistency across the types of studies

Men	AGRICAN cohort (Tual et al. Am J Epidemiol 2017)			Consortium 14 case-control studies (Synergy) (Pesch et al. Int J Cancer 2012)		
All lung cancers	N exposed cases	RR	CI95%	N exposed cases	RC	CI95%
Smoking history						
Never	41	1		220	1	
Former	275	8.66	6.24-12.02	3,496	7.50	6.50-8.70
Current	154	28.84	20.35-40.87	6,784	23.60	20.40-27.20
Pack-years of cigarettes						
Never	41	1		220	1	
<20	143	6.02	4.26-8.53	1,561	4.80	4.10-5.50
20-29	92	16.47	11.39-23.80	1,840	11.70	10.00-13.50
30-39	69	19.88	13.50-29.29	2,189	18.50	15.90-21.40
40-49	46	27.40	17.98-41.78	1,815	27.20	22.60-32.70
50-59	27	38.62	23.75-62.79	1,034	35.50	29.00-43.50
>60	37	37.37	23.94-58.31	1,741	40.00	32.80-48.50

Epidemiological complexity: interpretation of results

- What the non epidemiologists think and say
  - *« Results not statistically significant must not be considered »*
    - *P-value < 0.05*
- What epidemiologists know:
  - P-value =0.05 is **only a convention**
    - Risk to conclude wrongly to a difference
  - **No health risk to withdraw an occupational exposure**
    - but possible risk not to withdraw
  - Interpretation = deep **knowledge of the methods**

Occupational health: Necessity to consider trends when risks are elevated (p-value>0.05)
-> *Aim is not to be sure of the innocuity of a treatment but to avoid harmful exposures*

Epidemiological complexity: interpretation of results

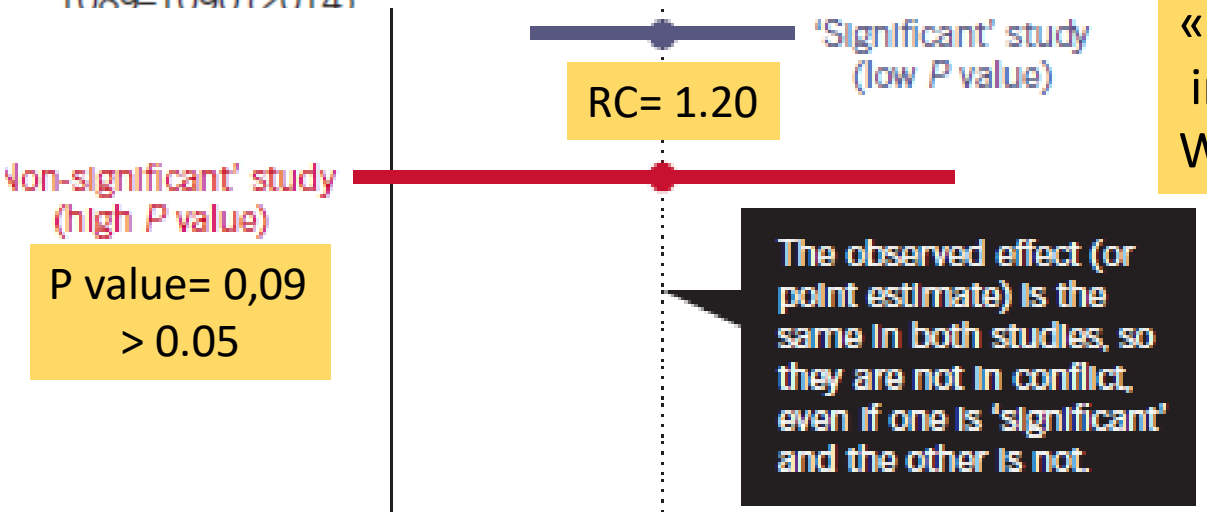
Retire statistical significance

Nature 21 Mars 2019

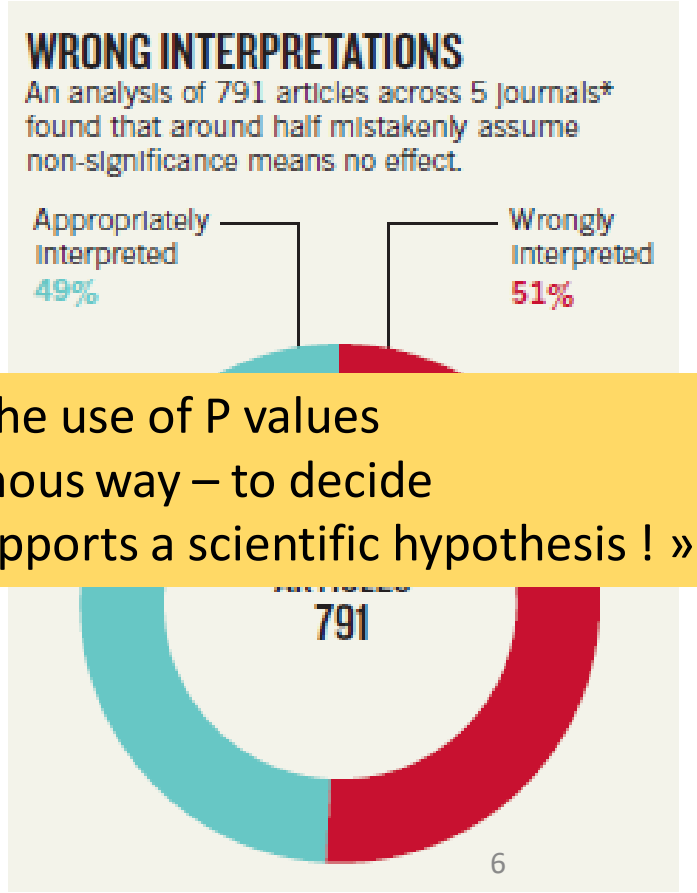
Valentin Amrhein, Sander Greenland, Blake McShane and more than 800 signatories call for an end to hyped claims and the dismissal of possibly crucial effects.

« In 2016, the *American Statistical association* released a statement In The *American Statistician* warning against the misuse of Statistical significance and P values »

2. Schmidt, M. & Rothman, K. J. *Int. J. Cardiol.* **177**, 1089–1090 (2014)



« We are calling for a stop to the use of P values in the conventional, dichotomous way – to decide Whether a result refutes or supports a scientific hypothesis ! »



Epidemiological complexity: interpretation of results

OXFORD ACADEMIC | Journals | Books

International Journal of Epidemiology

5 years Impact factor = 9.7

IEA International Epidemiological Association

Describing significance

In the *IJE*, we actively discourage the use of the term 'statistically significant' or just 'significant' and such statements in method sections as 'findings at P<0.05 were considered significant'. Please provide effect estimates with confidence intervals and exact P values, and refrain from using the term 'significant' in either the results or discussion sections of papers.

Our justification of this position is given in: Sterne J, Davey-Smith G. Sifting the evidence — What's wrong with significance tests? BMJ 2001; 322: 226-231. See also: Wasserstein RL, Lazar NA. The ASA's statement on P-values: context, process, and purpose. The American Statistician 2016: DOI: 10.1080/00031305.2016.1154108.

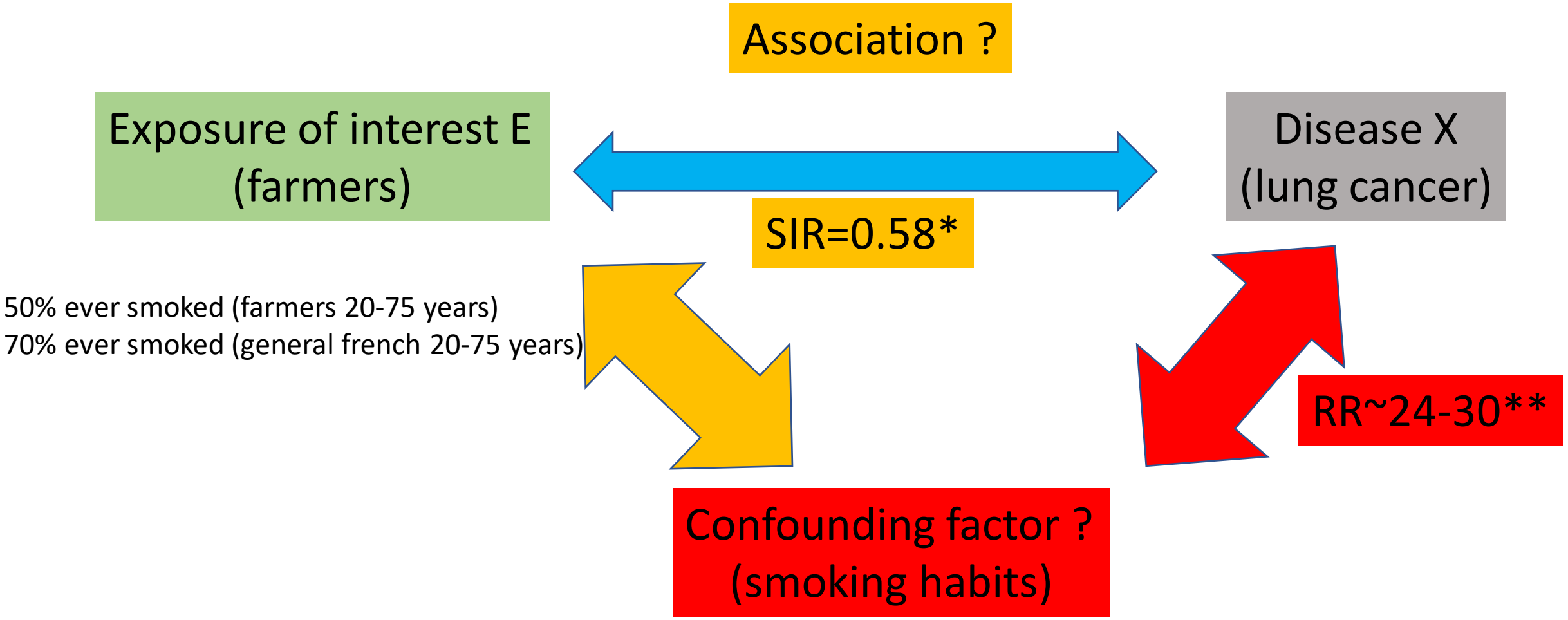
Epidemiological complexity: bias

- What the non epidemiologists think and say
  - *« Impossible to reach final conclusions because there are other parameters that can explain the links »*
- What epidemiologists know:
  - Risk of concluding wrongly is considered
  - Possibility of including many factors in the calculations (multivariate analysis)

Most biases (selection, information, confounding) can be controlled:
quality of study protocols, statistical methods

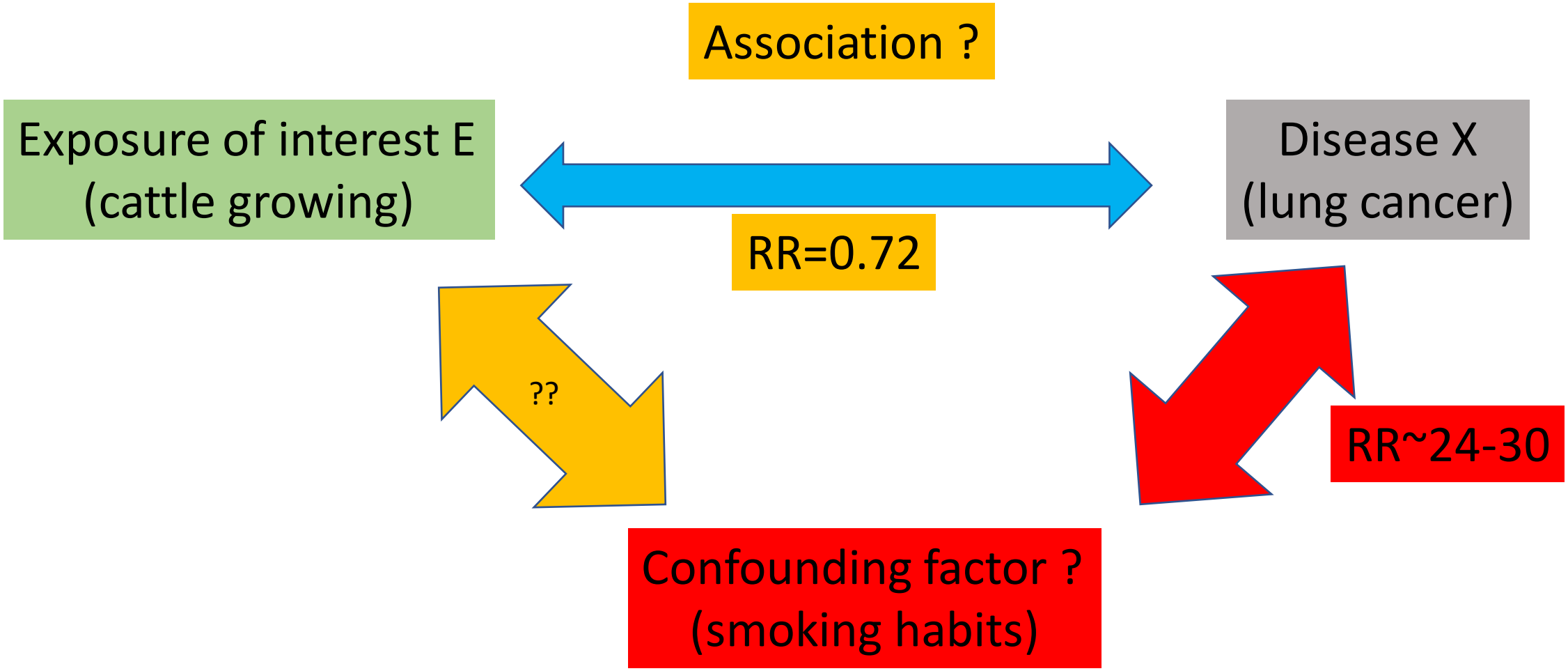
-> Epidemiology integrates the complexity of real life
*-> Conclusions represent **real conditions**: directly useful to populations*

Epidemiological complexity: confounding bias



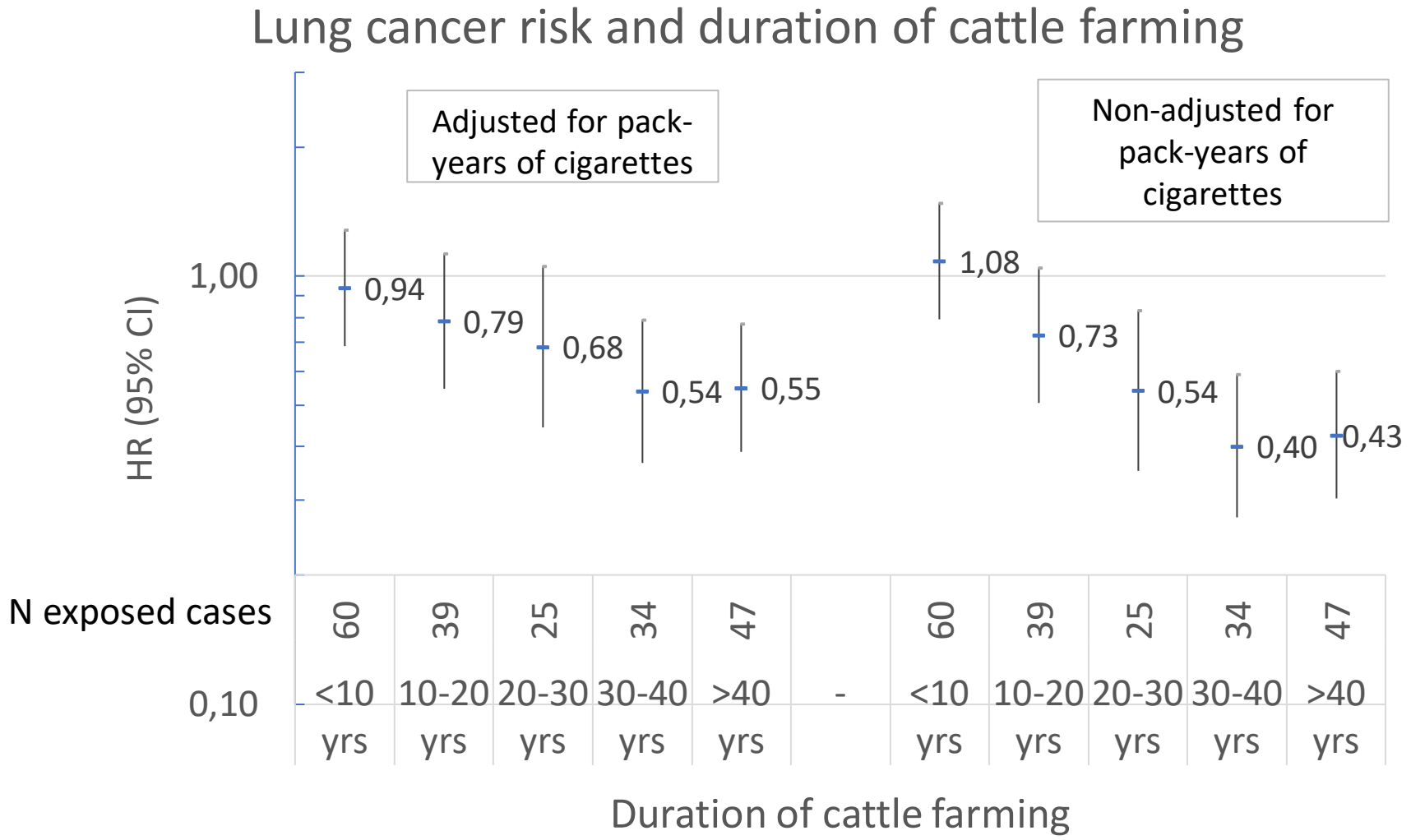
* Lemarchand et al. Cancer epidemiol 2017 / ** Tual et al Am J Epidemiol 2017 & Pesch et al. Int J Cancer 2012

Epidemiological complexity: confounding bias



Tual et al. Am J Epidemiol 2017 (AGRICAN data)

Epidemiological complexity: confounding bias



Tual et al. Am J Epidemiol 2017 (supplementary data for reviewers only)

Epidemiological complexity: information bias
Reliable exposure measurement by questionnaire (lifelong)

Variables	Activity or pesticide-related task					Start year			End year		
	PA (%)	Kappa	95% CI	PI	N	ICC	95% CI	N	ICC	95% CI	N
Grasslands[a]	81	0.53	0.44, 0.62	0.45	424	NA			NA		
Herbicide treatment[b]	76	0.45	0.34, 0.57	0.34	248	0.84	0.71, 0.92	35	0.97	0.95, 0.99	31
Wheat or barley[a]	83	0.64	0.56, 0.71	0.23	421	NA			NA		
Seed Treatment[b]	73	0.45	0.33, 0.58	0.08	199	0.96	0.94, 0.98	45	0.94	0.89, 0.97	41
Pesticide or herbicide treatment[b]	84	0.66	0.55, 0.77	0.24	199	0.97	0.94, 0.98	63	0.94	0.91, 0.97	59
Corn[a]	85	0.69	0.62, 0.76	0.17	417	NA			NA		
Seed Treatment[b]	75	0.06	− 0.12, 0.25	0.69	130			2			2
Pesticide or herbicide treatment[b]	88	0.71	0.58, 0.85	0.44	130	0.88	0.80, 0.93	54	0.94	0.90, 0.97	49

Tual et al. Cancer Causes & Control 2022

AGRICAN : low risk or dilution of risk (crude data on exposure) ?

Fruit growing and prostate cancer risk

In France in 2010s
Nb treatment/year=34
(23 Fung / 9 Ins / 2 Herb)

CANDINAVIAN JOURNAL OF WORK, ENVIRONMENT & HEALTH

Lemarchand et al. Scand J Work Environ Health (2016)

Epidemiological complexity: interpretation of results

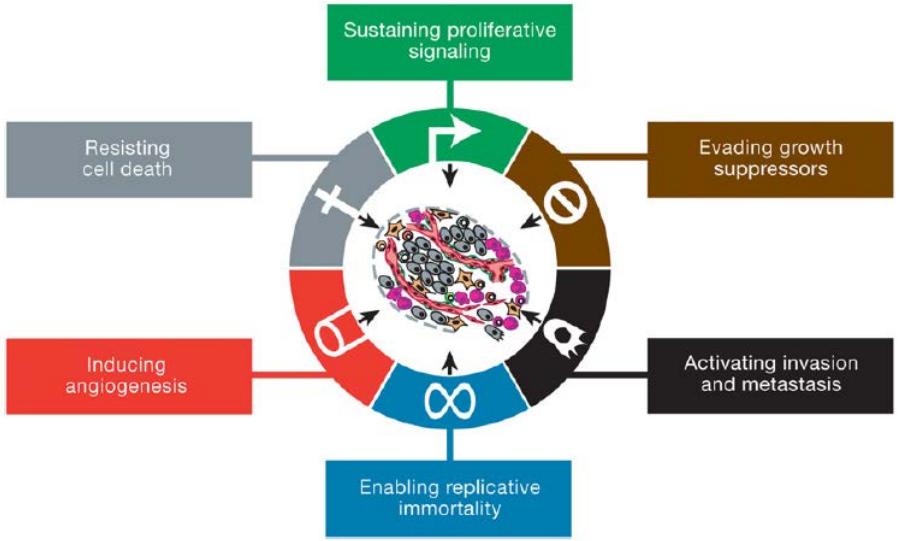
- What the non epidemiologists think and say

  « If there is no biological explanation to epidemiological results, they mustn't be considered »

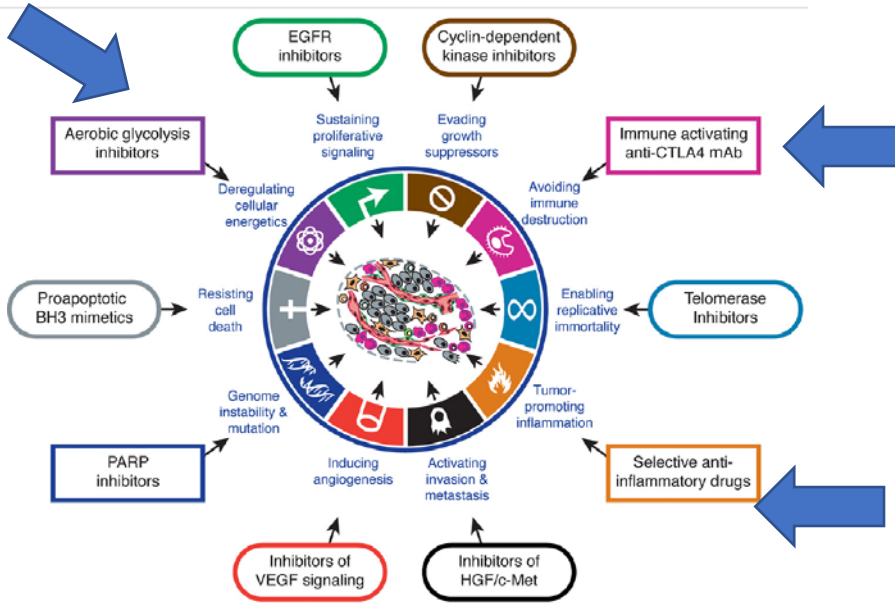
- What epidemiologists know:
- Mechanisms may be complex to identify
  - *Minamata disease & methylmercury*
  - *Arsenicals and cancer…*
- Unethical to wait for mechanisms knowledge if epidemiological results are consistent

Sometimes toxicological knowledge comes first, other times it is epidemiological knowledge
Biological plausibility is neither necessary neither sufficient for causality judgment
-> *Decisions can (must) be taken even if absence of mechanisms knowledge*

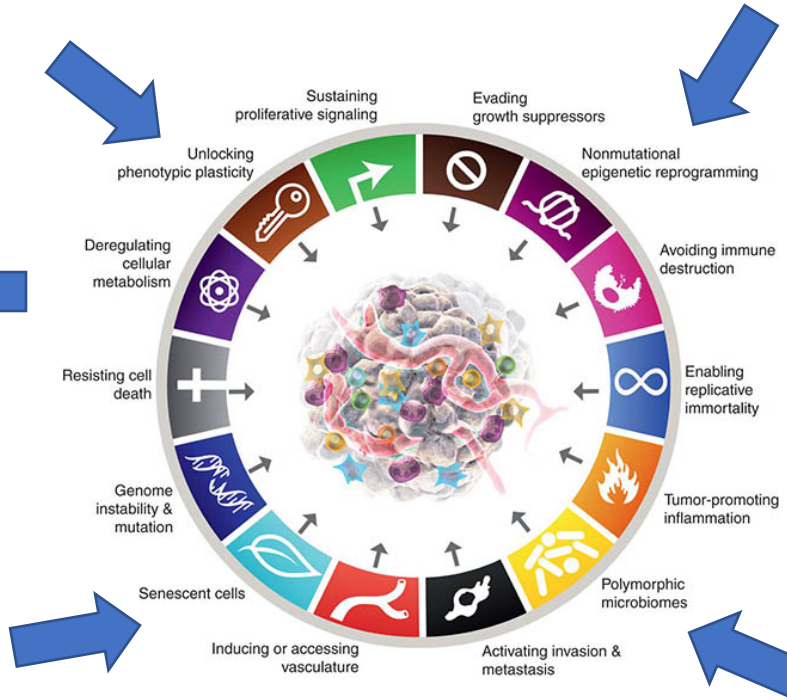
Epidemiological complexity: biological plausibility



Hallmarks of cancer in the 2000s
N=7



Hallmarks of cancer in the 2010s
N=10



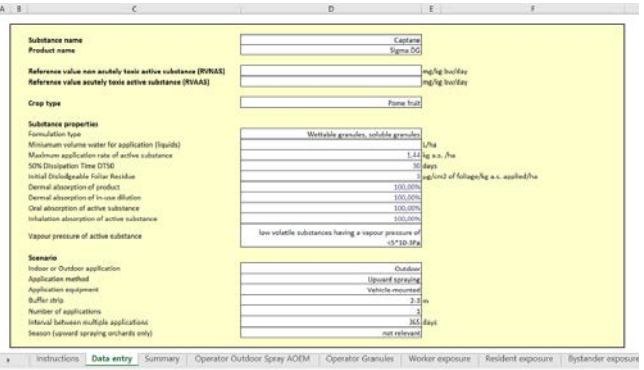
Hallmarks of cancer in the 2020s
N=14

Hanahan & Weinberg « Hallmarks of cancer: the next generation ».
Cell 2000 & 2011, Cancer discovery 2022

Take Home Messages

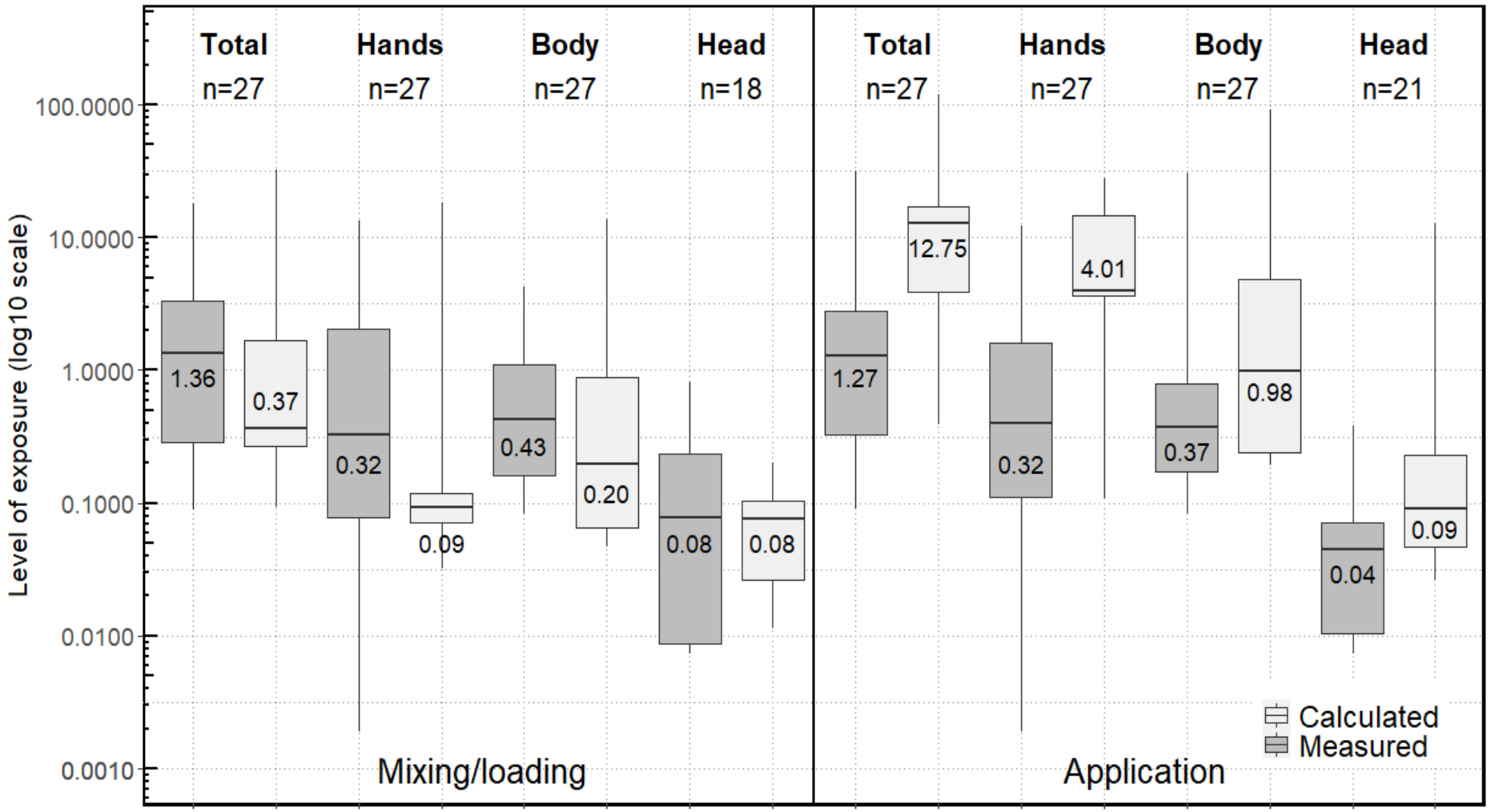
- Epidemiological methods are more complex than they seem and dealing with biases is our duty every single day
- Evaluation of observational epidemiological studies and their interpretation must be done by analytical epidemiologists even if discussion are necessary with risk assessors
  - Even most refined tools (for RoB…) cannot replace the knowledge of people who made the studies or those reviewing the papers
- Epidemiological (real life) results can provide causality judgement
- In Occupational Health, the aim is to avoid harmful exposures = even if $p>0.05$
- Many epidemiological results could be very useful in the view of pesticide regulation
- As well as field data on exposures that are generated to better assess exposures in epidemiological studies and compare with registration models….

Epidemiological results and registration models for operator exposure



Fruit growing
30 operators (poster)
2 fungicides (captan/dithianon)

Gardeners
X operators
Glyphosate (poster)



Overestimation of actual exposure of operators ?

Bresson et al. Int J Environ Res Public Health 2022 / De Graaf et al. (manuscript ongoing)

Prevention emerging from good epidemiological results

Relationship between specific crops and use of specific active ingredients of pesticide ?

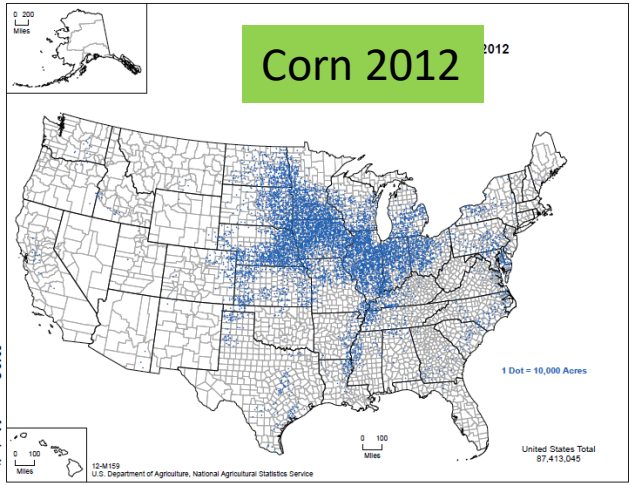
Some are very specific!

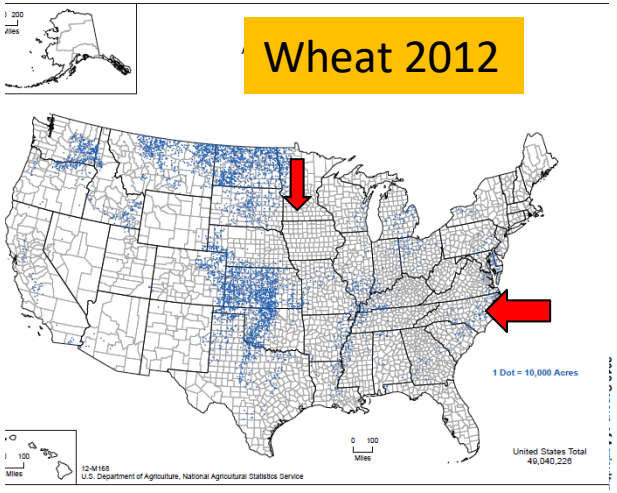
Apple trees and fungicid captan ; grapes and fungicid folpel ; wheat/barley and herbicide isoproturon… !

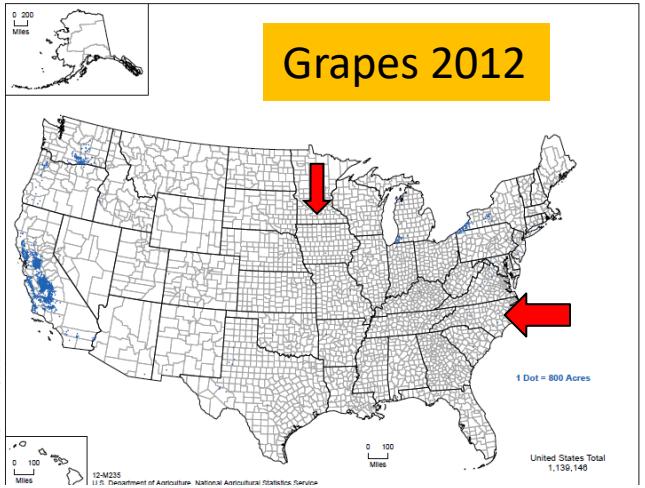
Some are less specific

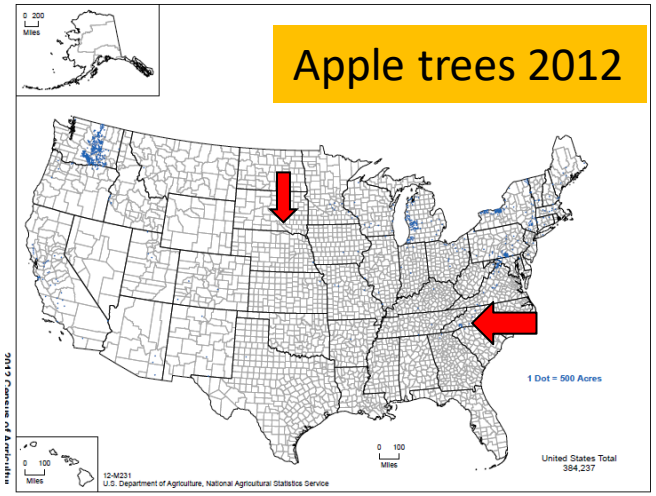
Relationship between specific agricultural practices (countries, type of soils…),
and type of pests and use of specific active ingredients of pesticide ?

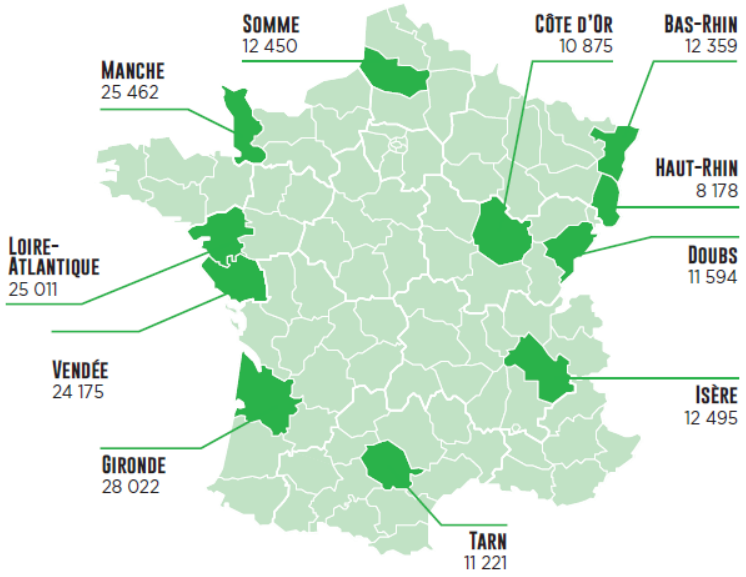
Prevention emerging from good epidemiological results

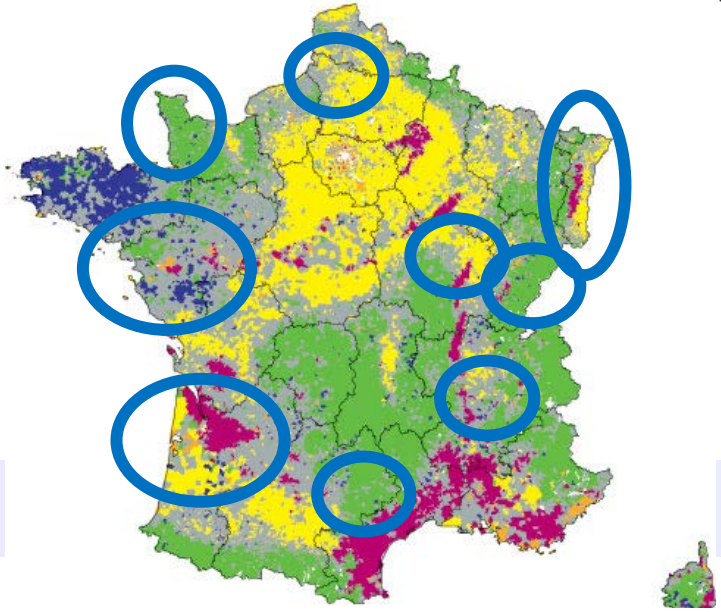












Open field
Vegetables
Grapes/fruit growing
Cattle/sheeps/horses
Poultry
Crops and livestock