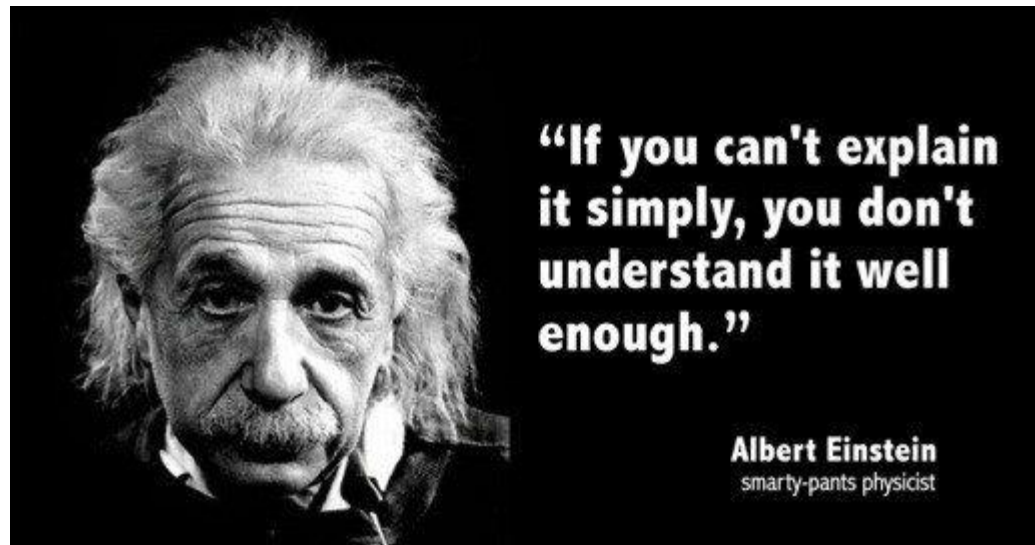


Use of epidemiological studies for chemical risk assessment

Þórhallur Ingi Halldórsson
Faculty of Food Science and Nutrition
University of Iceland
(tih@hi.is)

Suggestions on how epidemiology can be used for chemical risk assessment in 20 min!

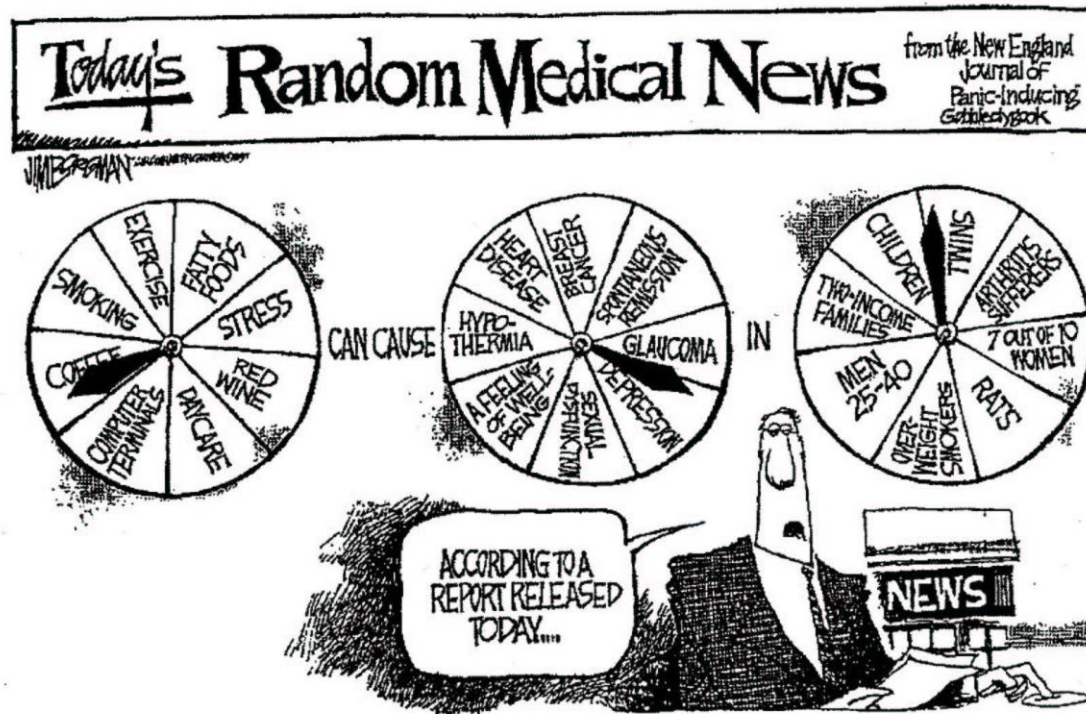
- I have no simple solutions



- Only a few thoughts....

Can we rely on epidemiological studies?

The “no” argument can easily be made



One view of the value of epidemiology

..and that argument is often made

Open access, freely available online

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

Summary

There is increasing concern that most current published research findings are false. The probability that a research claim is true may depend on study power and bias, the number of other studies on the

factors that influence this problem and some corollaries thereof.

Modeling the Framework for False Positive Findings

Several methodologists have pointed out [9–11] that the high

is characteristic of the field and can vary a lot depending on whether the field targets highly likely relationships or searches for only one or a few true relationships among thousands and millions of hypotheses that may be postulated. Let us also consider,

- A lot of problems identified with biomedical research, epidemiology in particular
- However, only ~13% of the paper is devoted to solutions

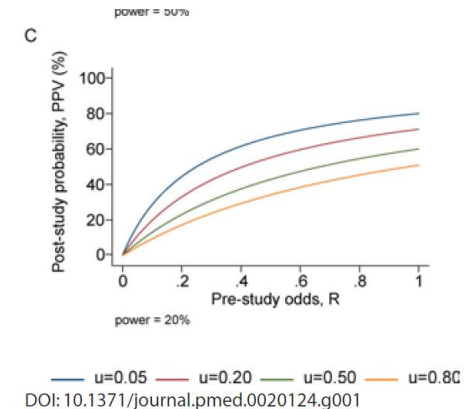


Figure 1. PPV (Probability That a Research Finding Is True) as a Function of the Pre-Study Odds for Various Levels of Bias, u . Panels correspond to power of 0.20, 0.50, and 0.80.

Similar arguments can be made for other disciplines

- **Poor quality** and reporting of animal studies
- compounds with little or no therapeutic potential proceed to clinical trials because overoptimistic conclusions are drawn about their efficacy as a result of flaws in experimental design and **bias**
- Given the large amount of animal research being undertaken, some findings will extrapolate to humans just by **chance**



Pandora Pound *medical sociologist*¹, Michael B Bracken *Susan Dwight Bliss professor of epidemiology*²

¹Bath, UK; ²Yale University Schools of Public Health and Medicine, New Haven CT, USA

How epidemiology can be used depends partly on the study design

- For chemical risk assessment we can mostly forget RCTs...
- ... but optimally we would like to all studies to be large scale **prospective cohort studies**
- Well conducted **case control** and **cross-sectional** studies can be (almost) equally as informative
- Ecological studies are hypothesis-generating

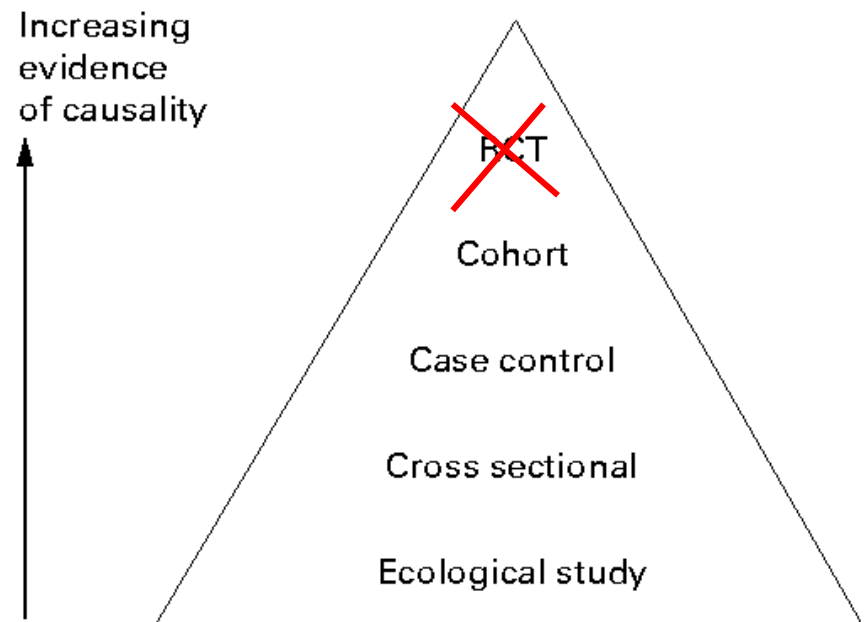


Figure 1 Pyramid showing hierarchy of study designs in determining causality.

It's the exposure

- **The main problem** is that in observational setting there is no control over the exposure including other co-exposures
- Which is not the case for controlled animal experiments



It's the exposure

- **The main problem** is that in observational setting there is no control over the exposure including other co-exposures
- Which is not the case for controlled animal experiments **but...**



≠



Quantifying the exposure

- Exposure has to be estimated using
 - **Surrogate measures** such as occupation, geographical locations. Quality depends on the research question.
 - **Subjective measures:** Yes/no, likely...unlikely. Prone to bias but it can work well, such as in occupational setting
 - **Objective measures:** such a blood or urine are generally more optimal. However, variation in uptake and excretion can be problematic



Virtually certain
Very likely
Likely
About as likely as not
Unlikely
Very unlikely
Exceptionally unlikely



The take home message (my opinion)

- **Confounding, publication bias, lack of power, multiple testing, self-reporting and other biases are problems that can be minimized in properly designed studies. They are perhaps secondary to....**
- **.... the quality of the exposure assessment.**

Essay

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The take home message

- **For chemical risk assessment the quality of the exposure largely determines how a study can be evaluated and interpreted**
- How the exposure is quantified does not always fit into established procedures used in risk assessment (developed around use of controlled studies in experimental animals).



Virtually certain

Very likely

Likely

About as likely as not

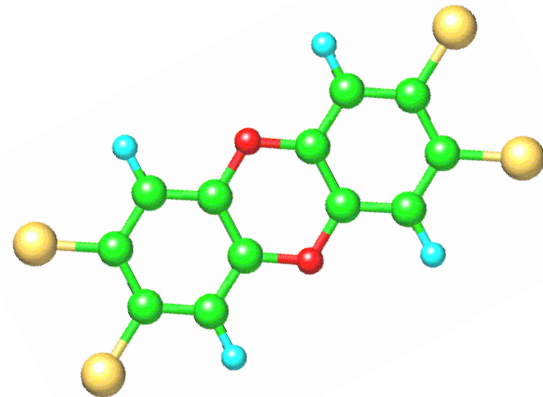
Unlikely

Very unlikely

Exceptionally unlikely



Let's look at a few examples



First example - Pesticides

studies that are difficult to use in risk assessment but receive allot of attention
(and generate allot of work for everyone)



Studies linking exposure to pesticides and health

Ntzani EE, Chondrogiorgi M,
Ntritsos G, Evangelou E, Tzoulaki I

EFSA supporting publication 2013:EN-497

EXTERNAL SCIENTIFIC REPORT

Literature review on epidemiological studies linking exposure to pesticides and health effects¹

Evangelia E Ntzani, Chondrogiorgi M, Ntritsos G, Evangelou E, Tzoulaki I

Department of Hygiene and Epidemiology, University of Ioannina Medical School, Ioannina, Greece

“...such epidemiological studies suffer from many limitations and that the heterogeneity of data is such that does not allow firm conclusions to be made.”

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“...such epidemiological studies suffer from many limitations and that the heterogeneity of data is such that does not allow firm conclusions to be made.”

“We also performed updated meta-analysis This has only been possible for childhood leukaemia and for Parkinsons disease. For both these outcomes we found significant associations between pesticide exposure and disease in line with previous evidence”

Exposure to pesticides during pregnancy and childhood leukaemia

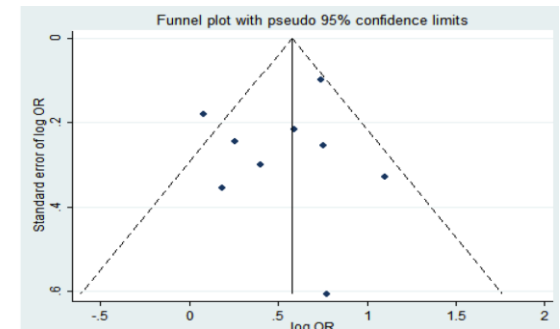
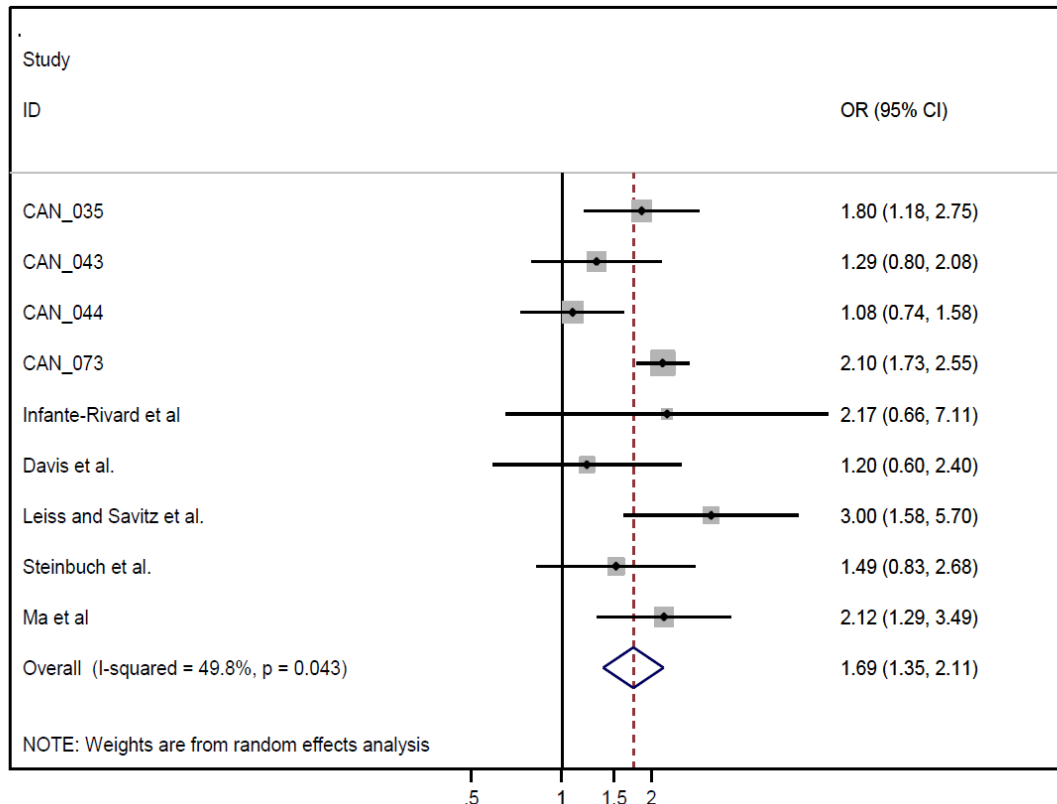


Figure 12: Random effects meta-analysis of the association between childhood leukemia and exposure to pesticides during pregnancy (Residential exposure to insecticide during pregnancy and childhood leukemia) (update to meta-analysis 2010 using published effect sizes; Turner 2010) and associated funnel plot

Limitations of these studies

- Lets ignore biases and all the usual suspects
- **They key issue in terms of using these studies is that we have no idea what chemicals the pregnant women were exposed to**
- And information on the duration and intensity of the exposure is also missing (perhaps less relevant)

Essay

Why Most Published Research Findings Are False

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Lets look at two studies (1)

- occupation as proxy for exposure -

Archives of Environmental & Occupational Health, Vol. 61, No. 3, 2006
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- Registry based case control study (1968-2000) in Northern England
- Examined risk of cancer during childhood was increased with **paternal** employment as recorded on the child's birth certificate!!
- farm owners and managers, forestry managers, horticulturists, gardeners, groundskeepers, horticultural trades, farm workers, forestry workers.

Paternal Occupational Exposure to Pesticides or Herbicides as Risk Factors for Cancer in Children and Young Adults: A Case-Control Study From the North of England

Mark S. Pearce, PhD; Donna M. Hammal, MSc; M. Tefvik Dorak, PhD;
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Our results do not support a role for preconception paternal occupational exposures to pesticides or herbicides in the etiology of childhood cancer

Let's look at two of these studies (2)

- self-reported exposure -

- ESCALE study (2003-2004), France.
Case control study
- Retrospective collection on conditions in pregnancy through telephone interviews
- Questions on pesticide exposure included
 - house- hold use of pesticides during pregnancy by the mother and father.
 - Insecticides used at home (pets, garden crops); herbicides (weed killers); and fungicides
 - Exposure to pesticides at work during pregnancy (incl agricultural occupation)
 - The questionnaire also detailed residential history since conception.



Household Exposure to Pesticides and Risk of Childhood Hematopoietic Malignancies: The ESCALE Study (SFCE)

Author(s): Jérémie Rudant, Florence Menegaux, Guy Leverger, André Baruchel, Brigitte Nelken, Yves Bertrand, Catherine Patte, Hélène Pacquement, Cécile Vérité, Alain Robert, Gérard Michel, Geneviève Margueritte, Virginie Gandemer, Denis Hémon and Jacqueline Clavel

Source: *Environmental Health Perspectives*, Vol. 115, No. 12 (Dec., 2007), pp. 1787-1793

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Source: *Environmental Health Perspectives*, Vol. 115, No. 12 (Dec., 2007), pp. 1787-1793

The consistency of the findings with those of previous studies on AL raises the question of the advisability of preventing pesticide use by pregnant women

Main weaknesses

- Paternal occupation as proxy for pregnancy exposure!!
- Perhaps valid in some cases but?
- Self-reported data are prone to bias but is still more informative than using paternal occupation.
- Differences in how case and control mothers assess past exposures ?

Archives of Environmental & Occupational Health, Vol. 61, No. 3, 2006
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What do these studies on pesticides and childhood leukaemia say?

- Being potentially exposed to pesticides during pregnancy is associated with childhood leukaemia
 - What chemical may account for this (if any) is unknown
 - Role of confounding and other biases cannot be excluded



**Are these studies good examples
of “bad science”?**



A hypothetical example

Let's say that several studies would report association between frequent use (self-report) of household cleaning products and miscarriage (or fetal death).



A hypothetical example

- Such studies would be considered of public health relevance, despite limitations.
- In comparison with pesticides less energy would be spent on finding out if the causal agent (if any) was, for example, some constituent in:



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- In comparison with pesticides less energy would be spent on finding out if the causal agent (if any) was, for example, some constituent in:



OR



A hypothetical example

The aim of epidemiological studies is not always to produce results compatible with formal toxicological risk assessment





OR




“Low quality“ studies have initiated a lot of relevant work

- In terms of exploring alternative testing methods
- ...and call for improvements

EVENT REPORT  

APPROVED: 9 March 2017
doi:10.2903/sp.efsa.2017.EN-1191

Workshop Report on integrated approach for testing and assessment of developmental neurotoxicity
European Food Safety Authority and OECD


European Food Safety Authority

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31 October 2017

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Pesticides: how can risk assessors make better use of epidemiological data?



EFSA's pesticide experts have developed an approach that could help risk assessors to make better use of epidemiological data in the assessment of active chemical substances used in pesticides.

“Low quality“ studies have initiated allot of relevant work

- Improving quality is possible
- But it requires
 - better sharing of data between suppliers, users and researchers
 - **Human biomonitoring** (to assess residential exposures).
 - **Patience but not panic**

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Home News Pesticides: how can risk assessors make be...
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Pesticides: how can risk assessors make better use of epidemiological data?



EFSA's pesticide experts have developed an approach that could help risk assessors to make better use of epidemiological data in the assessment of active chemical substances used in pesticides.

Better studies will be published but the working environment is difficult



003.02.20. Residential Proximity to Agricultural Herbicides during Pregnancy and Childhood Leukemia in the Danish National Birth Cohort

Deven Patel

Deven Patel¹, Steen Gyldenkærne², Rena R. Jones¹, Thomas Becker², Sjurdur Olsen³, Chalotta Granström³, Leslie T. Stayner⁴, Mary H. Ward¹

- This is the first prospective study to evaluate residential proximity to pesticide applications and childhood cancer
- ~10.000 birth and 61 leukaemia (AL) cases
- Addresses during the pregnancy to crop maps and crop-specific pesticide sales data applied 100, 250, 500, 1000m of homes
- Associations for several compounds but not

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-



NYHEDER TOPHISTORIER 31. AUGUST 2018



Ny forskning: Pesticider godkendt i Danmark mistænkt for at være kræftfremkaldende

31. AUG. 2018 KL. 15:27

Second example: Food additives correlated dietary exposures, what to do?



How to interpret epidemiological studies on food additives

- Sweeteners
- Other additives
- ...including “boring“ old ones like nitrite and nitrate

ARTICLE

doi:10.1038/nature13793

Artificial sweeteners induce glucose intolerance by altering the gut microbiota

Jotham Suez¹, Tal Korem^{2*}, David Zeevi^{2*}, Gili Zilberman-Schapiro^{1*}, Christoph A. Thaiss¹, Ori Maza¹, David Israeli³, Niv Zmora^{3,4,5,6}, Shlomit Gilad¹, Adina Weinberger², Yael Kuperman², Alon Harmelin⁶, Ilana Kolodkin-Gal², Hagit Shapiro¹, Zamir Halpern^{2,6}, Eran Segal² & Eran Elinav⁷



So how can information from such studies be used?

SCIENTIFIC OPINION



ADOPTED: 12 July 2017

doi: 10.2903/j.efsa.2017.4971

Guidance on the use of the weight of evidence approach in scientific assessments

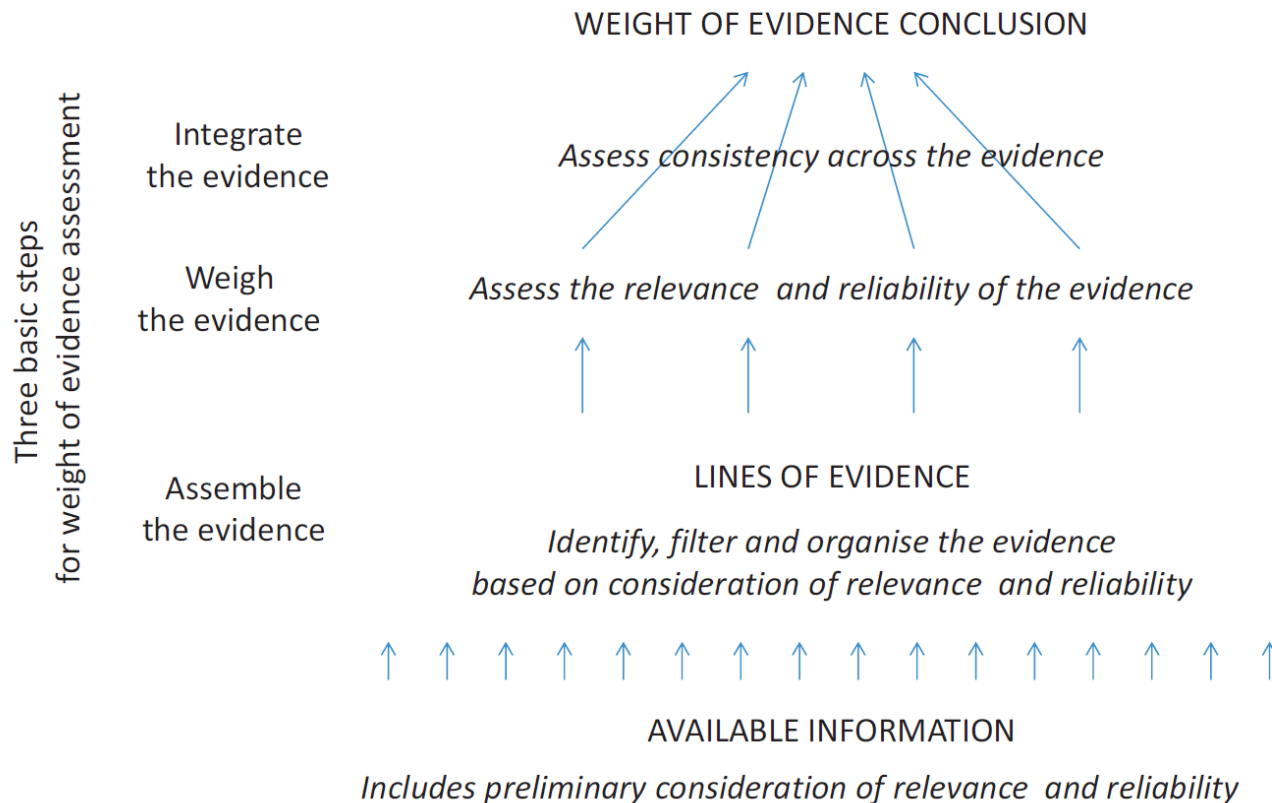
EFSA Scientific Committee,

Anthony Hardy, Diane Benford, Thorhallur Halldorsson, Michael John Jeger, Helle Katrine Knutsen, Simon More, Hanspeter Naegeli, Hubert Noteborn, Colin Ockleford, Antonia Ricci, Guido Rychen, Josef R Schlatter, Vittorio Silano, Roland Solecki, Dominique Turck, Emilio Benfenati, Qasim Mohammad Chaudhry, Peter Craig, Geoff Frampton, Matthias Greiner, Andrew Hart, Christer Hogstrand, Claude Lambre, Robert Luttik, David Makowski, Alfonso Siani, Helene Wahlstroem, Jaime Aguilera, Jean-Lou Dorne, Antonio Fernandez Dumont, Michaela Hempen, Silvia Valtueña Martínez, Laura Martino, Camilla Smeraldi, Andrea Terron, Nikolaos Georgiadis and Maged Younes

Weight of evidence

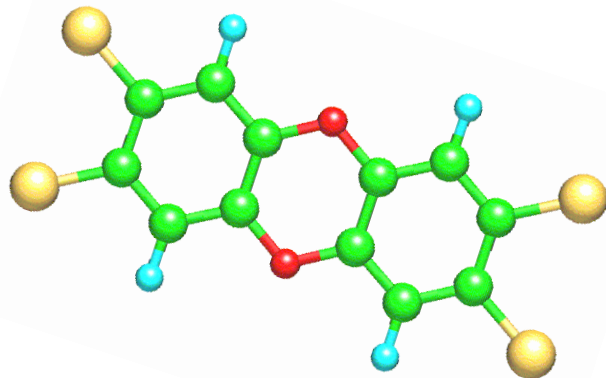
Clear guidance exists but we could be better at implementing it at times.....

Guidance on the weight of evidence



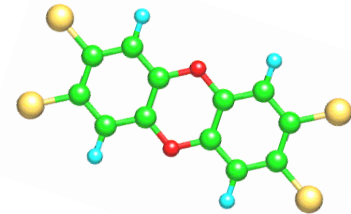
Third and final example

studies where individual exposure can be assessed more accurately (through biomarkers)



Biomarkers of exposure

- Numerous chemicals can be accurately quantified at low sample volume and cost in blood and urine
- PCBs, PFAS, Hg, Pb, ...As, Bis-A, phthalates, phenols....
- The non-persistent ones are a bit problematic (several measurements are needed)
- Epidemiological findings are increasingly being used for risk assessment for such chemicals.



Use of observational studies for chemical risk assessment is in principle not complicated

SCIENTIFIC OPINION

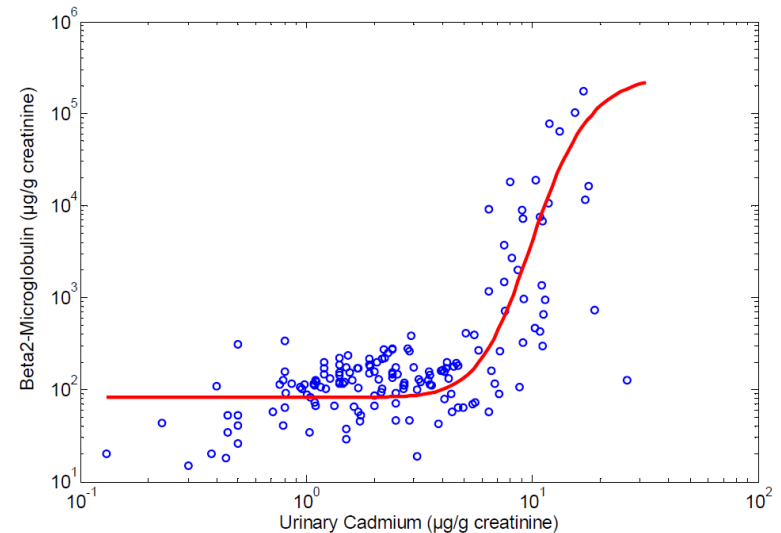
Cadmium in food¹

Scientific Opinion of the Panel on Contaminants in the Food Chain

(Question No EFSA-Q-2007-138)

Adopted on 30 January 2009

other examples perchlorate, nickel, arsenic



But we have to be careful

- Confounding and other potential biases need to be considered carefully
- Wrong interpretations/decisions may have unfavorable consequences
- One study no matter how spectacular, only tells a limited story

The New England Journal of Medicine

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Volume 333

NOVEMBER 23, 1995

Number 21

TERATOGENICITY OF HIGH VITAMIN A INTAKE

KENNETH J. ROTHMAN, DR.P.H., LYNN L. MOORE, D.SC., MARTHA R. SINGER, M.P.H., R.D.,
UYEN-SA D.T. NGUYEN, M.P.H., SALVATORE MANNINO, M.D., M.P.H.,
AND AUBREY MILUNSKY, M.B., B.CH., D.SC.

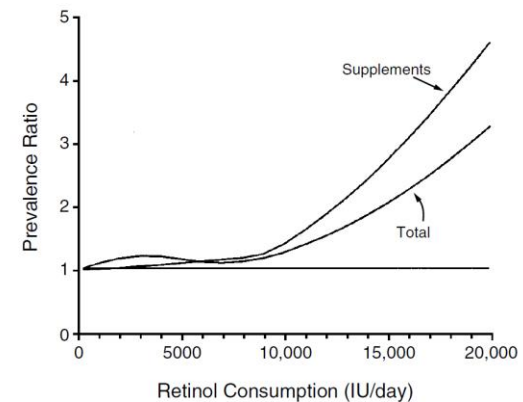
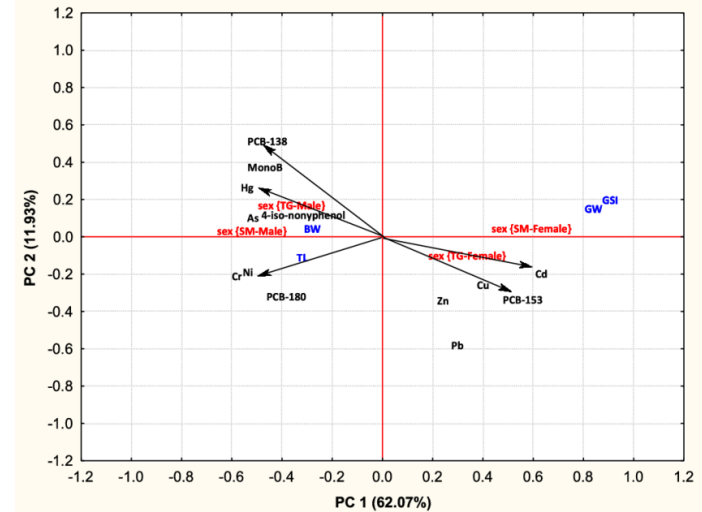


Figure 1. Estimated Prevalence Ratio for Birth Defects Related to the Cranial Neural Crest, According to Retinol Intake during the First Trimester of Pregnancy.

We also need to remember ...

- **That human observational studies do not fit into the same box as controlled animal studies**
- And we need deal practically with the absence of controlled conditions
 - co-exposures
 - zero dose!!
 - how HBGV are derived
- it is possible

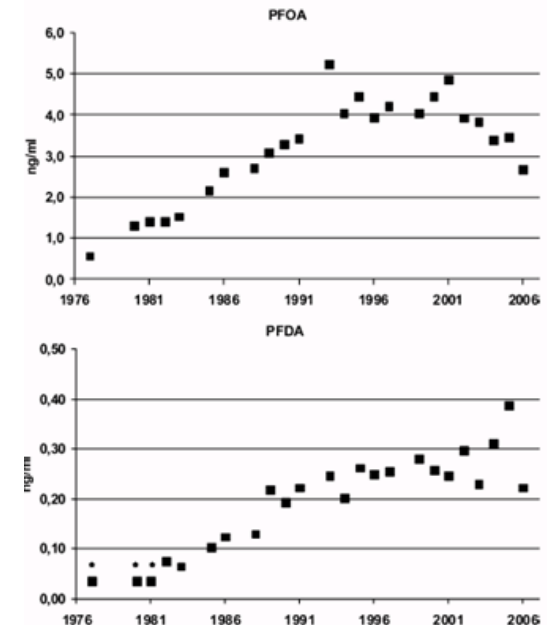
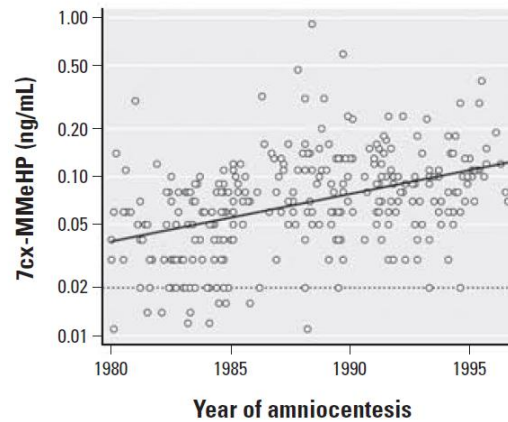
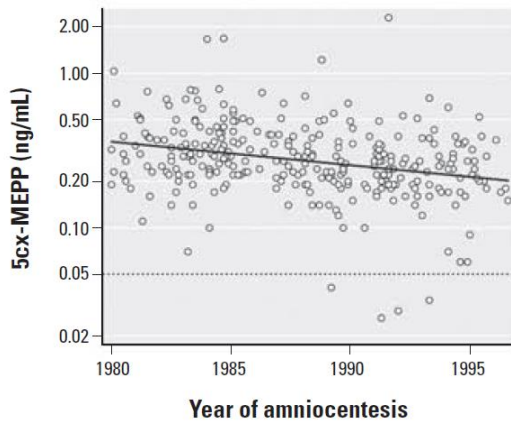


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Environmental epidemiology is a game of cat and mouse

- And sometimes there is no mouse (or no cat for that matter)
- Levels are not static and they are partly influenced by research intensity, independent of any risk assessment



Conclusion

- Poor exposure assessment can make use of epidemiological studies problematic.
- Despite those limitations careful interpretations of study findings are informative and should be included in the weight of evidence approach
- When exposure can be accurately assessed, integration of epidemiological studies is in principle not complex.
- Human observational studies will never tick into the same boxes as controlled animal experiments
- Better understanding between toxicology and epidemiology is needed



Thank you

You Can Fail & Not Be Guilty



5% of You Will

