Use of epidemiological studies for chemical risk assessment

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

- I have no simple solutions

“If you can't explain it simply, you don't understand it well enough.”

Albert Einstein
geny-pants physicist

- Only a few thoughts....
Can we rely on epidemiological studies?

The "no" argument can easily be made.
A lot of problems identified with biomedical research, epidemiology in particular

However, only ~13% of the paper is devoted to solutions
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...

- 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 often works well such as in occupational setting.
  - Objective measures such as blood or urine. Variation in uptake and excretion can be problematic.
Quantifying the exposure

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  - **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 as blood or urine are generally more optimal. However, variation in uptake and excretion can be problematic
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.
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).
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

"...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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“We also performed updated meta-analysis ..... This has only been possible for childhood leukaemia and for Parkinson’s 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)
Lets look at two studies (1) - occupation as proxy for exposure -

- 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.
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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. Tevfik Doruk, PhD; Richard J.Q. McNally, PhD; Louise Parker, PhD

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 Paquement, 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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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?
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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  OR

  OR
A hypothetical example

The aim of epidemiological studies is not always to produce results compatible with formal toxicological risk assessment
“Low quality“ studies have initiated a lot of relevant work

• In terms of exploring alternative testing methods

• ...and call for improvements
“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
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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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
How can epidemiological studies be used in such cases?

- In principle additives from food can be quantified using existing dietary methods.

- However, even if we studies could derive such intake estimates (in mg/day) for E131, E251/252, E951, E955, ....

- It would not be a major improvement from just looking at the main food contributors.

- **Dietary variables are not independent of each other**

- But there are established ways to work around that, which differs from the approached taken in most chemical risk assessment.
So how can information from such studies be used?
Weight of evidence

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

Guidance on the weight of evidence

Three basic steps for weight of evidence assessment

Integrate the evidence

Weigh the evidence

Assemble the evidence

WEIGHT OF EVIDENCE CONCLUSION

Assess consistency across the evidence

Assess the relevance and reliability of the evidence

LINES OF EVIDENCE

Identify, filter and organise the evidence based on consideration of relevance and reliability

AVAILABLE INFORMATION

Includes preliminary consideration of relevance and reliability
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.

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
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
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