Systematic Reviews, Machine Learning and the Liberation of Knowledge from Information in Environmental Health Research

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Lancaster Environment Centre | Lancaster University | ebtc | Johns Hopkins Bloomberg School of Public Health

About me

- Researcher at Lancaster University and the Evidence-Based Toxicology Collaboration at Johns Hopkins Bloomberg School of Public Health
- Background in environmental health NGO advocacy and science communication, now working in chemical risk assessment, primarily around developing and advocating use of systematic methods in chemical risk research
- Associate Editor for Systematic Reviews at Environment International (IF 7.297)
- The “frameworks guy” in systematic review methods for environmental health research: systematic approaches to evidence surveillance and synthesis; critical appraisal tools; codes of practice; quality assurance and control
- Not a computer scientist, moving in the direction of machine learning anyway

What I'm going to talk about

- Winning the argument about using systematic review methods, but…
- …neglecting to mention the data volume problem
- Machines should read scientific documents into graph databases
  - Even simple graph databases are pretty neat: e.g. data-driven AOPs
  - Large databases are really neat: chemical and disease signatures
- How non-computer-scientists can help machines learn to read
- Pay-off: we can capture the sum total state of human knowledge

Systematic review methods in chemical risk assessment

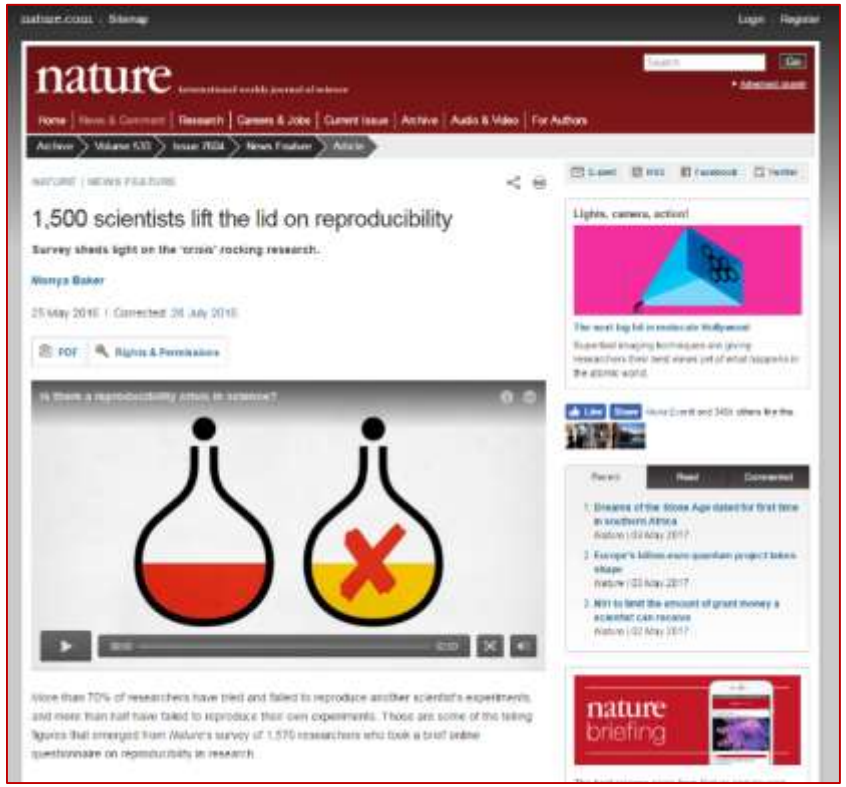
The data volume problem

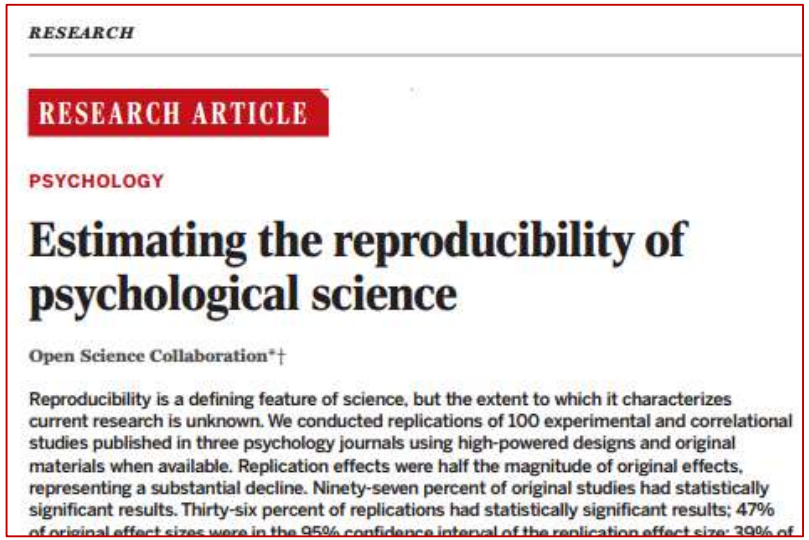
Graph databases

What non-computer scientists can do

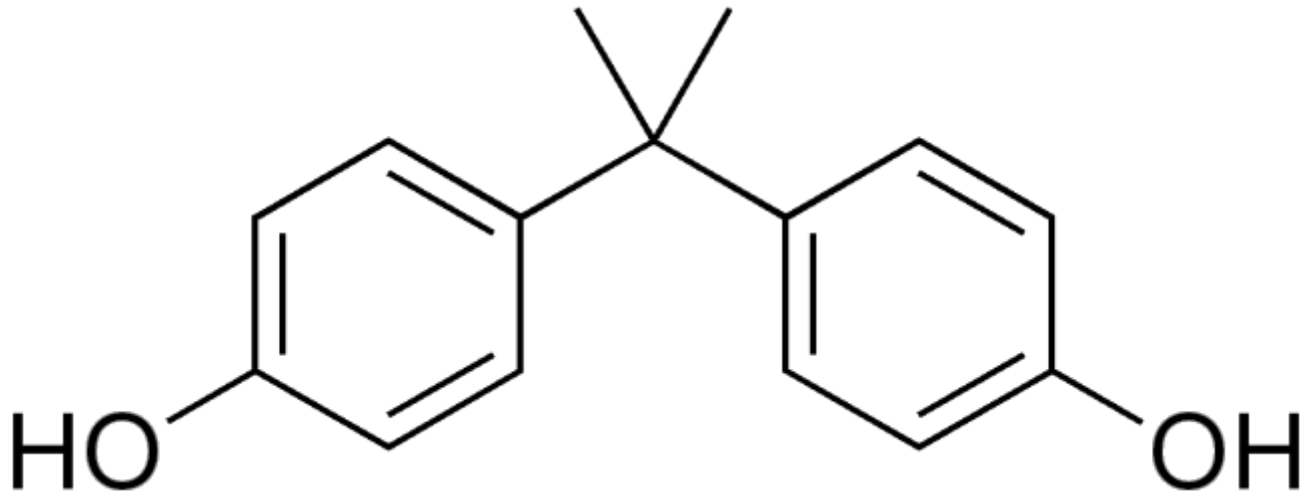
The pay-off

Reproducibility crisis in primary research



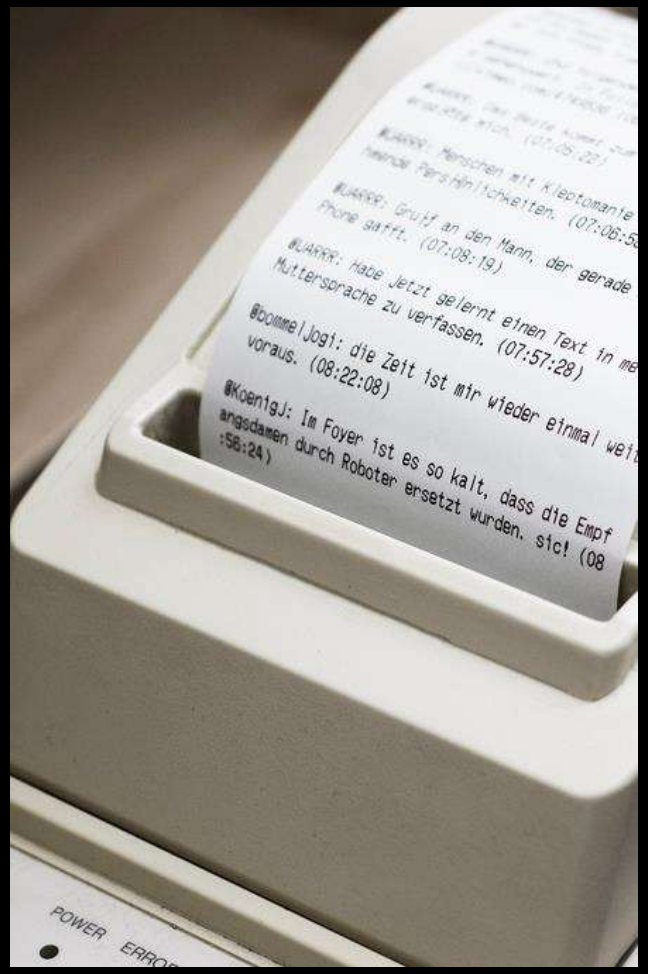


Reproducibility crisis in risk assessment?



Bisphenol-A


Shanks Fin Soup
Bumble Bee
Pink Salmon
Ligo
Squid


@boomeljogi: die Zeit ist mir wieder einmal
voraus. (08:22:08)
@KoenigJ: Im Foyer ist es so kalt, dass die Empf
angsdamen durch Roboter ersetzt wurden. stc! (08
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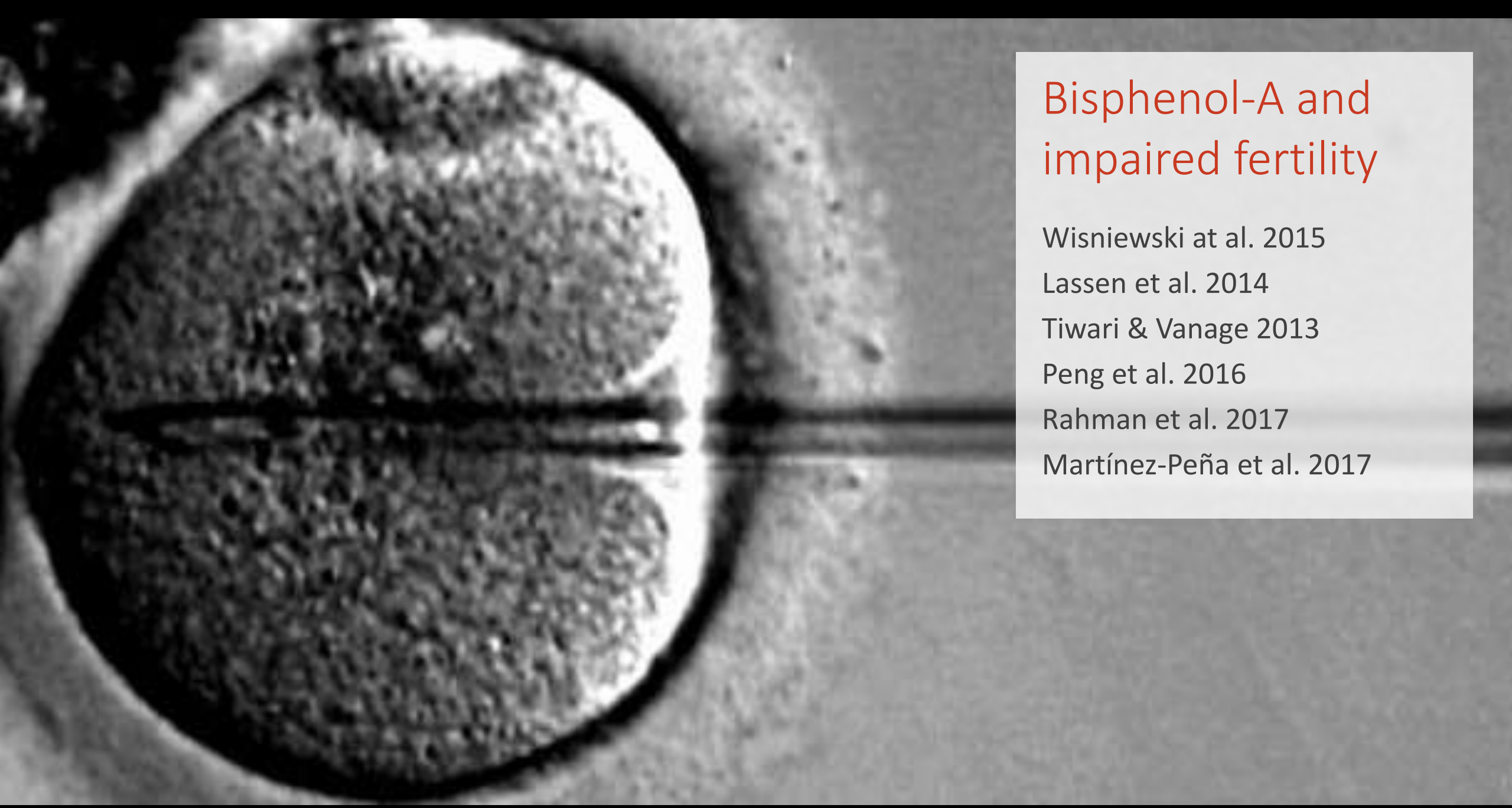
POWER



Bisphenol-A and impaired fertility

Wisniewski at al. 2015

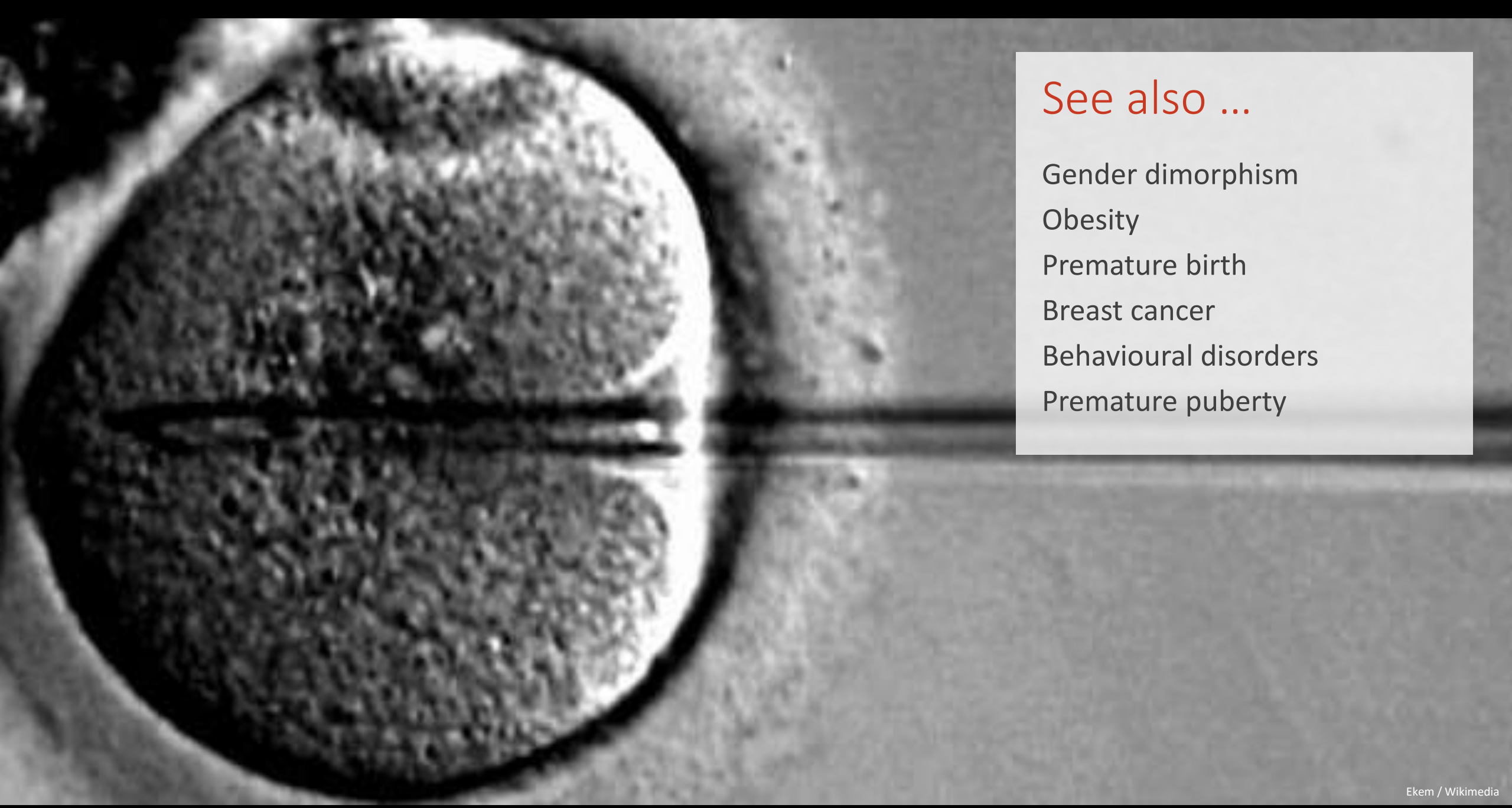
Lassen et al. 2014

Tiwari & Vanage 2013

Peng et al. 2016

Rahman et al. 2017

Martínez-Peña et al. 2017



See also …

Gender dimorphism

Obesity

Premature birth

Breast cancer

Behavioural disorders

Premature puberty

Ekem / Wikimedia

efsa
European Food Safety Authority

Public Health England

FDA

KAROLINSKA INSTITUTET ANNO 1810
Karolinska Institutet

International Agency Research on Cancer

World Health Organization

…effects have been demonstrated for BPA [at] levels **10–10,000x lower** than the current LOAEL of 50 mg/kg/day

Vandenberg et al. 2014

…**no health concern** for any age group from dietary exposure

EFSA 2015

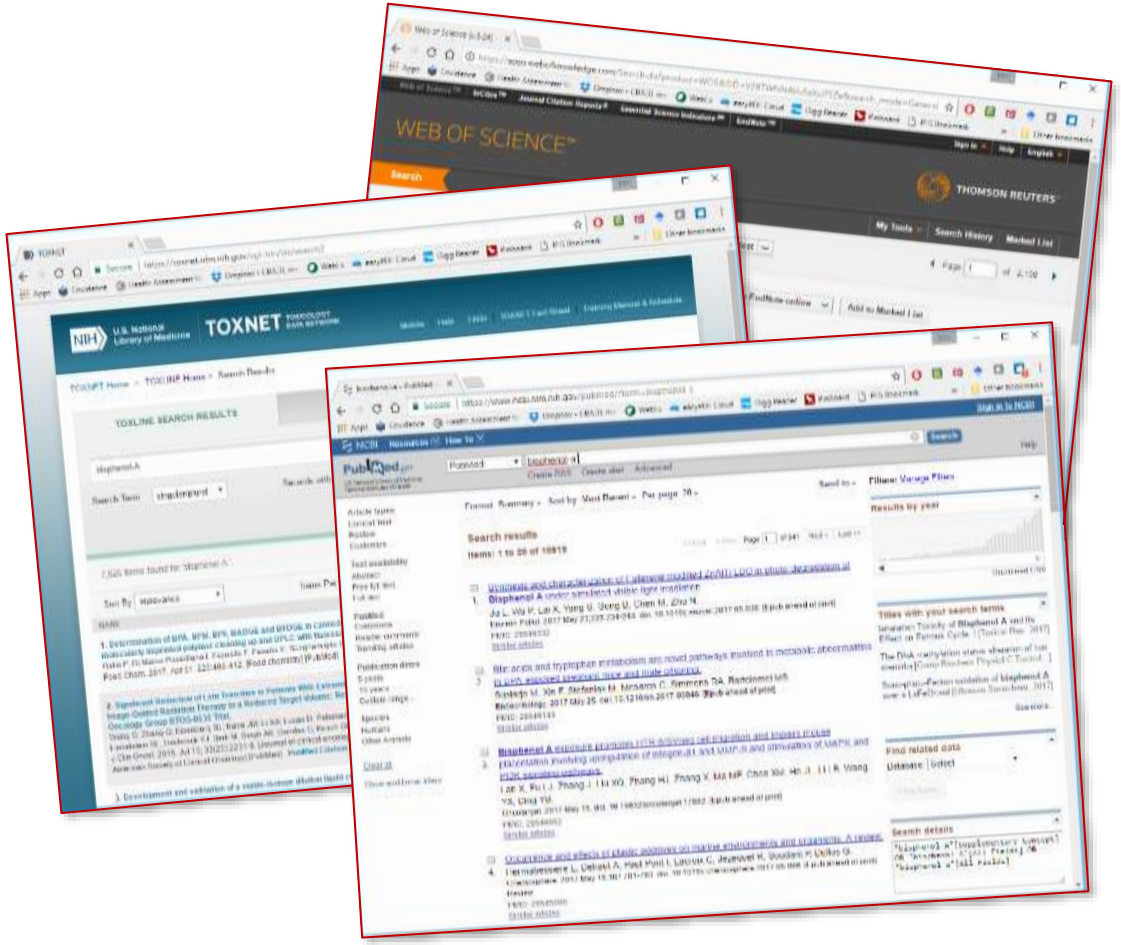
…a TDI for BPA has to be **0.7 µg/kg bw/day** or lower to be sufficiently protective

National Food Institute, Denmark 2015

…a **potential risk to the unborn children** of exposed pregnant women [relating to] a change in the structure of the mammary gland

ANSES 2013

Same evidence, different conclusions



?

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National Food Institute, Denmark 201

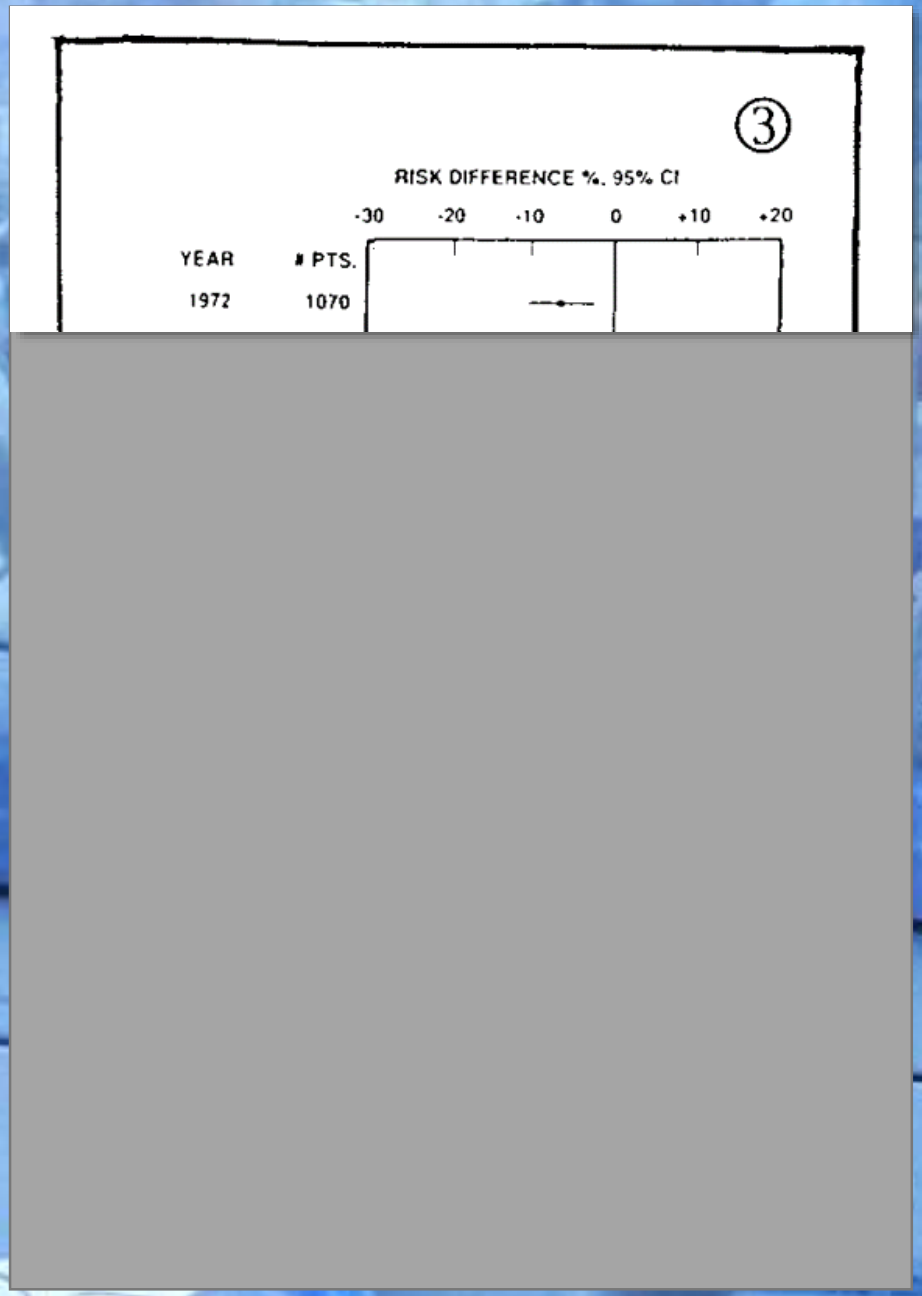
…effects have been demonstrated for BPA [at] levels **10–10,000x lower** than the current LOAEL of 50 mg/kg/day
Vandenberg et al. 2014

What can we do about this?

- Medicine has already seen this problem and come up with a solution
- We can borrow that

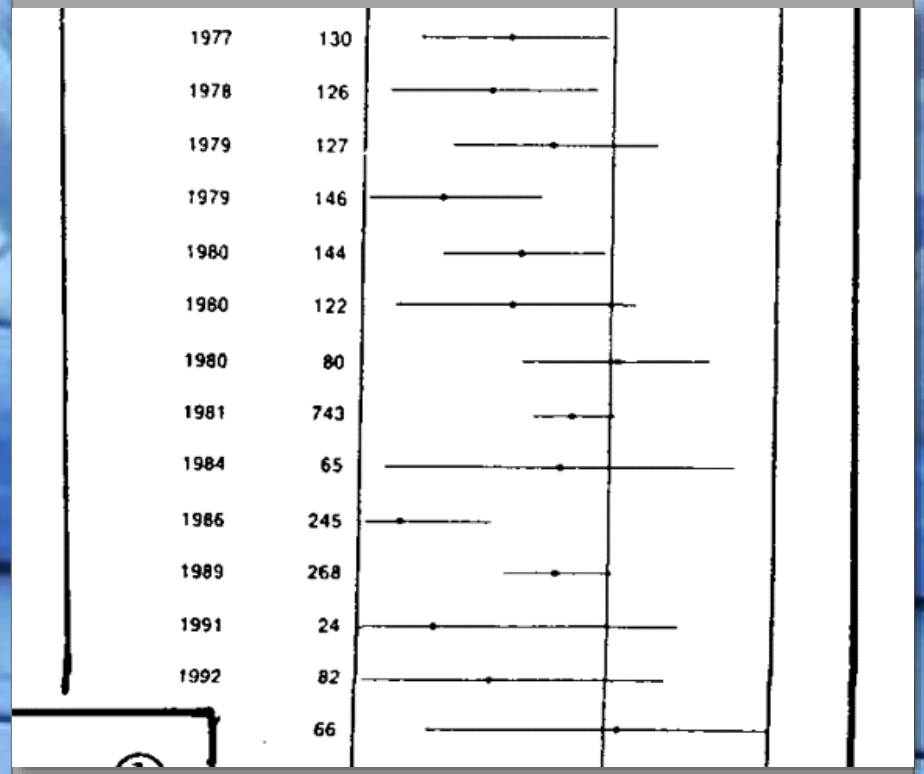
Steroids and premature birth

- Infants born prematurely are at increased risk of life-threatening respiratory distress syndrome
- 1970s: Could risk be reduced by giving a dose of steroids to women expecting to give birth prematurely?



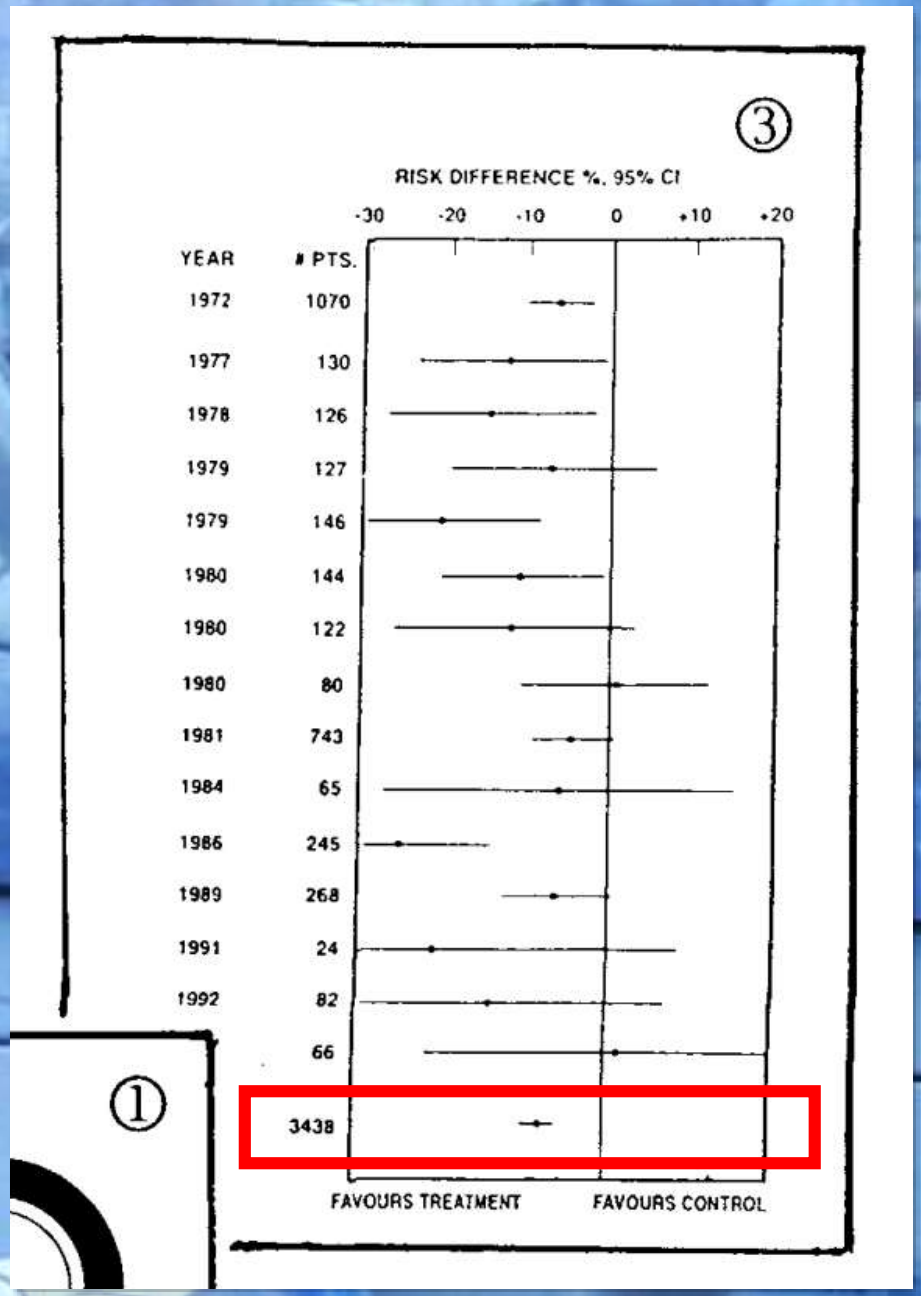
Steroids and premature birth

- 1972: large trial shows steroids reduce mortality in premature birth



Steroids and premature birth

- 1977-1993: More trials, small and individually unconvincing, lots of differences between studies
- Divided expert opinion



Steroids and premature birth

- 1994: All studies aggregated in a systematic review, showing clear benefit
- 22 years wasted: we should already have known
- Unethical to conduct unnecessary studies

Success of systematic review in medicine

- Major role in resolving a lot of debates and uncertainty about what the evidence says about the effectiveness of medical treatments
- Systematic reviews are the most-cited type of research in the medical literature and form the evidence base for medical guidelines worldwide
- **Can we apply SR methods and get the same benefits when assessing health risks posed by chemical substances?**

What does it mean to be systematic?

- To use transparent, reproducible methods for reviewing what existing evidence says in answer to a research question, in a process which minimises the risk that the results of the review will be biased

Elevating the literature review to the status of a science

Three hallmarks of the scientific method

- Transparency: document everything (exhaustively)
- Reproducibility: two different research teams should be able to get the same results (or if not, at least be able to explain why not)
- Truthfulness: results should be unbiased (as free as possible from systematic error)

Three sources of bias in reviewing evidence

- Bias arising from flaws in the design, conduct, analysis and reporting of included studies being transmitted through to the results of a review (bias from limitations in the evidence)
- Bias due to systematic differences in results between the retrievable and irretrievable evidence (publication bias)
- Bias from conduct of the review itself, e.g.
  - Selective use of evidence (using part rather than all of the evidence base)
  - Selective interpretation of the evidence (seeing what you want / expect)

Systematic methods help prevent bias

- Pre-planned protocol defining review methodology
- Comprehensive search strategy
- Screening search results for relevance against objective criteria
- Comprehensive data extraction
- Critical appraisal of the included studies (risk of bias assessment)
- Valid qualitative and quantitative methods for synthesis
- Valid methods for interpreting confidence in results

Systematic methods compare favourably with expert-led approaches

Uptake of SR methods in chemical risk and environmental health research

- 2008: Arguably first mooted by Hartung and Hoffmann (EBTC)
- 2014: First SR guidance documents for EH research (UCSF Navigation Guide and NTP/OHAT)
- 2015: First journal Special Issue dedicated to SR methods in CRA
- 2016: First specialist SR editor at an environment health journal
- 2017: Next WHO/ILO Global Burden of Disease estimate to be based on 18 SRs, with pre-published protocols; EFSA bases a risk assessment (BPA) on SR methods for first time
- 2018: WHO protocols published; US EPA and GRADE Special Issues initiated; second editor
- SR described in EFSA, ECHA, NTP, EPA, TCEQ guidance. In legal text for identification of EDCs in EU. NGOs, agencies, industry and academia all support these methods.

Systematic review methods in chemical risk assessment

The data volume problem

Graph databases

What non-computer scientists can do

The pay-off

We have to review a lot of research

- It takes about 18 months to systematically review a few dozen studies
  - Planning
  - Searching and screening
  - Extraction of relevant data
  - Reporting
- Only small systematic reviews are feasible
  - Focus on a single exposure/outcome pair to keep data volume down
- Thousands of chemicals need assessing with systematic methods
- Data volume problem gets worse as in vitro testing is mainstreamed

The problem with focus

- Excludes relevant evidence e.g. BPA+1, which seems silly
  - It is relevant, just indirectly so: we know structural similarities between chemicals can inform risk estimates
  - But including BPA+1 increases evidence by orders of magnitude
- Risk management questions are rarely so focused
  - Need comprehensive view of evidence relating to potential health risks
  - Many health end-points, mixed exposures, etc.

Computers will have to read for us

- Managing the data volume problem by excluding it
- To maintain systematic standards **and** take advantage of all the data we already have and generate every day, we need to hand over the reading of documents to computers


EDITLIB
NEIN

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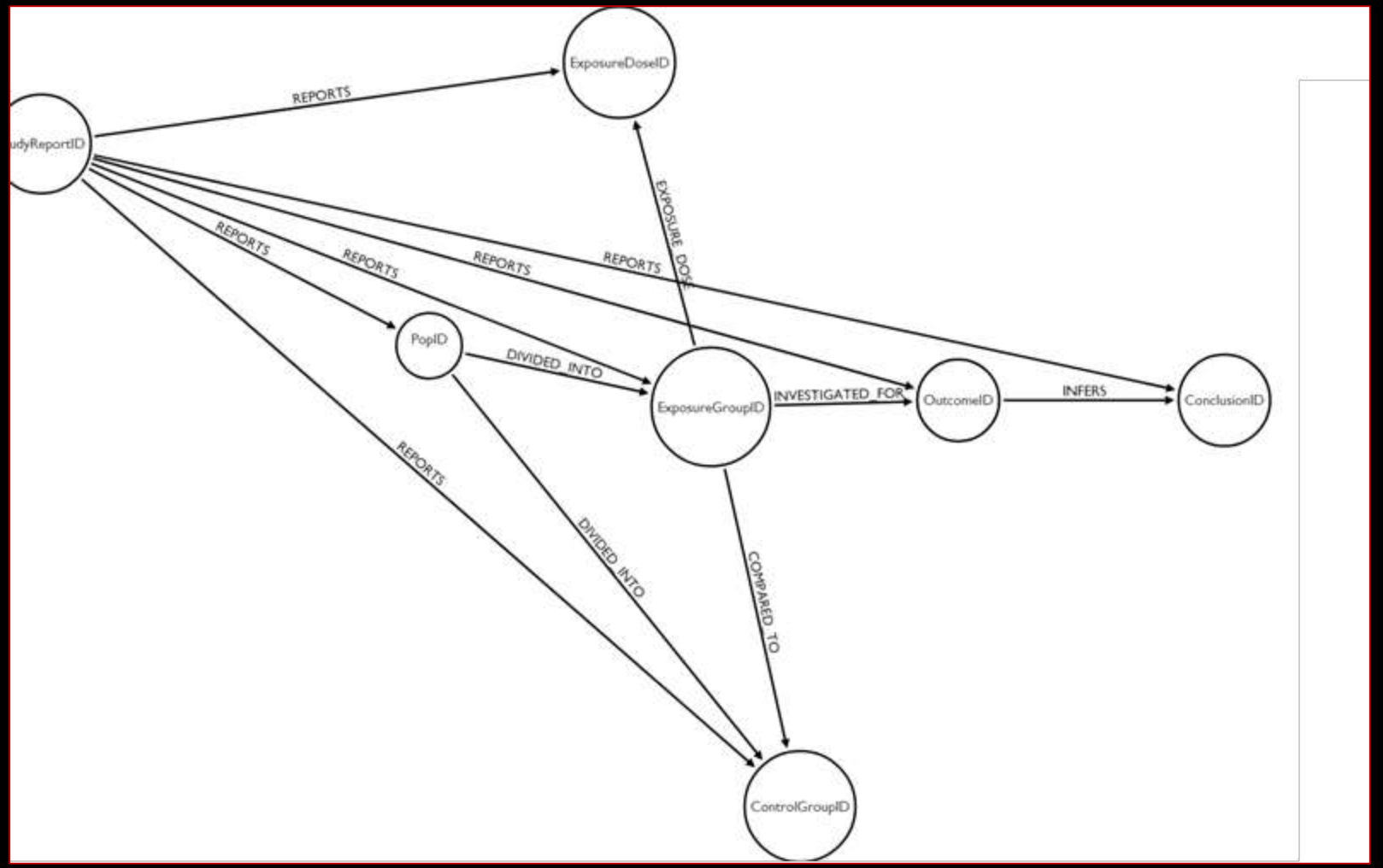
Data infrastructures for machine reading

- Currently, summarise studies as tables, or as tables with primary keys and relationships (relational DBs)
- Requires us to figure out how to represent all the information in a document in a relational scheme. Hard work.
- Also, small number of relationships; crudely summarised to get key queries working, but a poor imitation of real complexity in the data
- Since how things are related is something we are discovering all the time, relational databases are not a great engineering solution to storing data contained in scientific documents

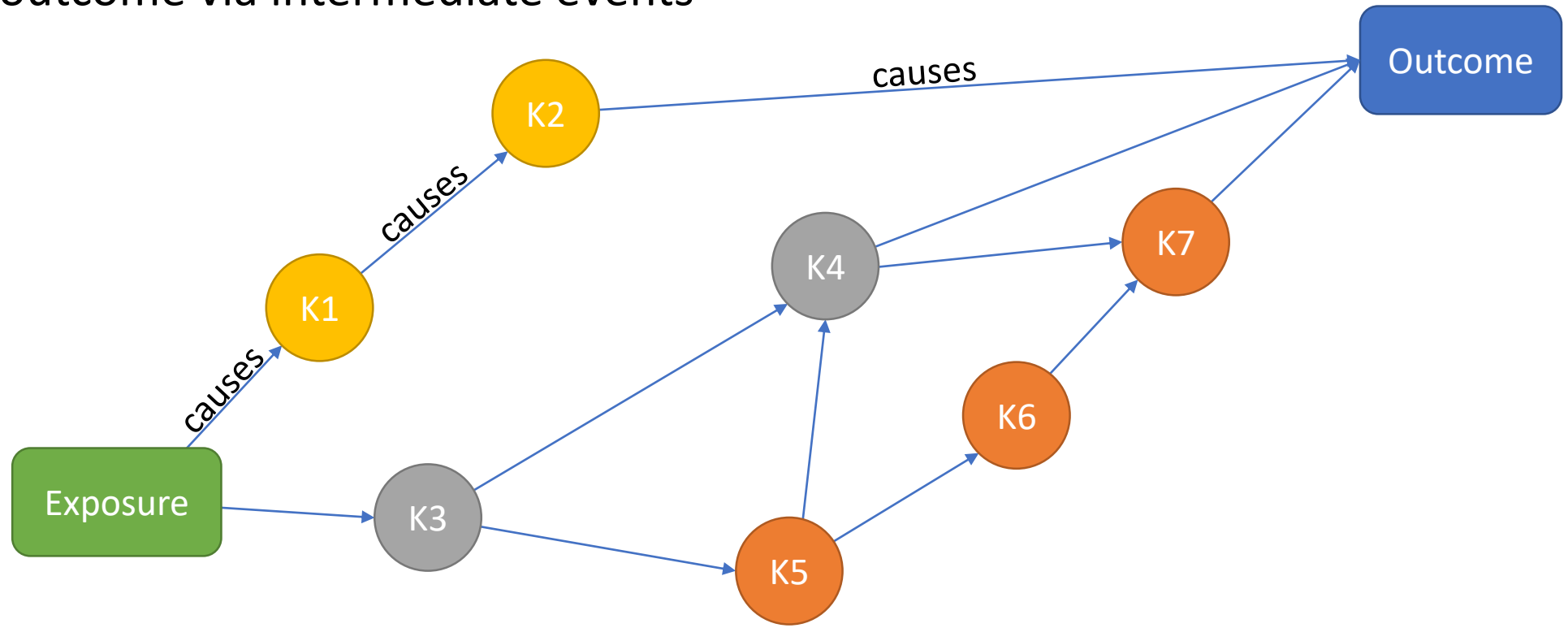
There is a better way: semantic databases

- Most of what is going on in research can be represented or summarised in a finite set of subject-predicate-object triples
  - Rat group | IS DOSED WITH | BPA
  - BPA | CONCENTRATION IS | 5 mg/kgbw/d
  - Rat group | INVESTIGATED FOR | liver tumors
  - Liver tumors | SHOW | increase
- Graph databases are built direct from these triples


ExposureDoseID
REPORTS
udyReportID
EXPOSURE_DOSE
REPORTS
REPORTS
REPORTS
REPORTS
PopID
DIVIDED_INTO
ExposureGroupID
INVESTIGATED_FOR
OutcomeID
INFERS
ConclusionID
REPORTS
DIVIDED_INTO
COMPARED_TO
ControlGroupID

Adverse Outcome Pathways and graphs

- AOPs are increasingly important for predicting health outcomes from environmental exposures, connecting exposures and initiating events through to outcome via intermediate events

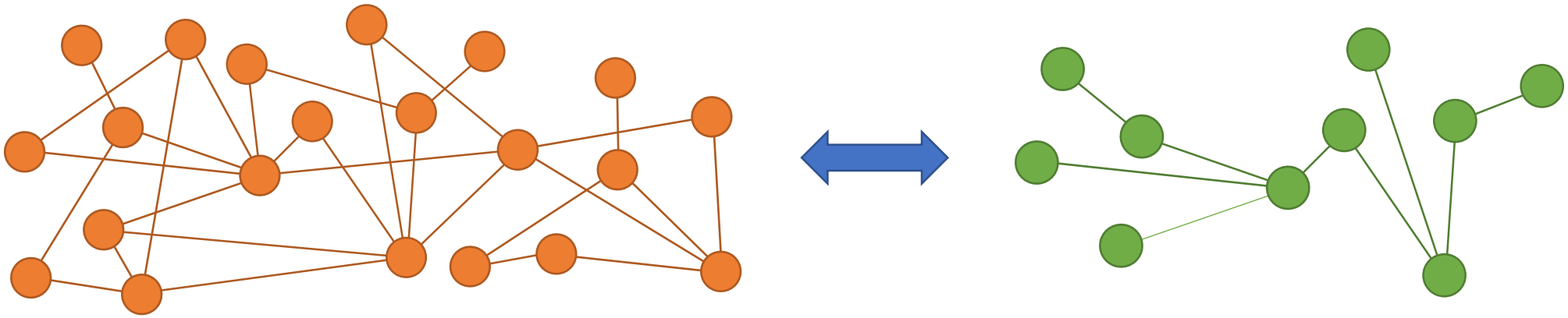


Data-driven AOPs

- Networks of events which are incompletely presented or investigated in any given document
- A systematic, data-driven approach would be to read all literature about chemicals and events, and map the relations
- Not practical: Too big a job: thousands of events, hundreds of thousands of documents
- Machine learning makes the data-driven identification of AOPs possible, and at least positions the relevant data in situ even if it needs a human to analyse it

Eventually, chemical and disease signatures

- Lots of data atoms, and relations between them, creates a big, inter-related space in which chemicals start having signatures.
- Compare the signature of a PFAS to carcinogenicity; RA disappears as we know it, probabilistic assessment takes its place



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Prerequisites of effective, automated SR

- More supervised learning (annotated corpora), especially for tasks like recognising causal claims: requires domain expertise
- Stuff like changing publishing practices (what is it with tables?)
  - Remove needless impediments to making research machine-readable
- No point in automating the generation of biased results
  - Better reporting practices so we understand the quality of the input data (garbage in / garbage out: already a big problem in SRs, mega-problem when machines read studies into mega-databases
  - Validity of the methods we are automating, e.g. risk of bias, strength of evidence assessment in GRADE

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The pay-off

Humans are silly, part nine million

- We already have a database of all written knowledge, it just consists of millions of isolated documents unevenly distributed across millions of square kilometres of digital and physical space
- We query this database by looking for documents, reading them, trying to remember the bits that matter to us, and ignoring the bits that don’t
- Reports of these queries are more self-contained documents, which are added to the pile of documents which are unevenly distributed across physical and digital space, which someone has to read, etc. etc.
- Someone else with different information requirements then reads a bunch of these documents again, ignores and remembers different bits, produces a report which is another document, etc. and so forth

The pay-off

- ML and graphs allow a formal representation of state of human knowledge, not just a bunch of data points in isolated PDFs
- The machines take care of making data accessible; frees up humans to make best use of what we do know, and figure out how to find out what we don’t know. (e.g. documents around the data-driven AOP)
- As a systematic reviewer, it entirely puts me out of a job, of course. See you on the beach!

Thank you for listening!