

Association and Causation: a Bradford Hill approach to Aerotoxics Syndrome.

David Gee

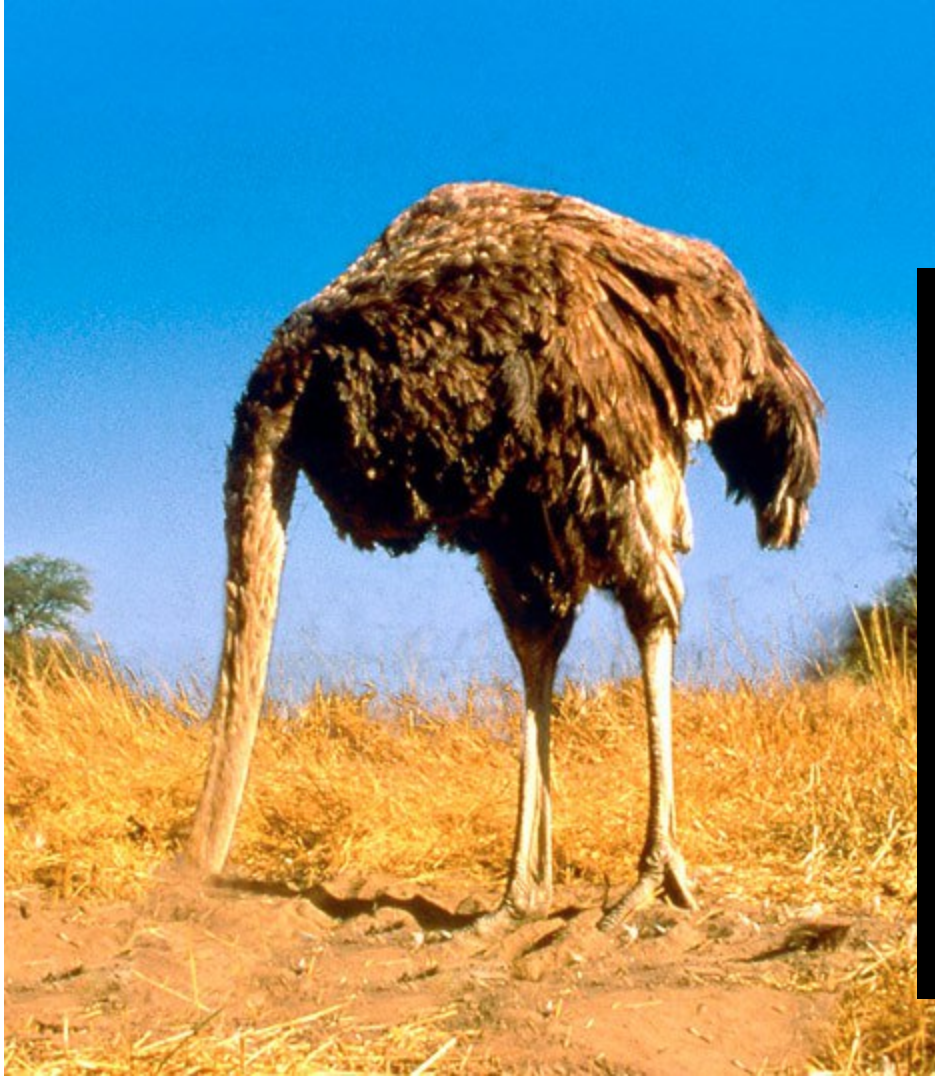
Visiting Fellow , Institute of Environment, Health & Societies,
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London AS conference, Sept 19/20, 2017.

Lord Keynes on changing one's mind...

When the facts change I change my mind.....

What do you do, Sir?"



Summary

- *“Late Lessons from Early Warnings” 1895-2015:some insights*
- *“Why do businesses not react to early warnings?”*
- *“Seattle: we have a problem”*
- *“You are not alone”: similarities between AS and 34 other Hazards.*
- *“Surprise comes to the prepared mind” & “consider continuums”*
- *The Bradford Hill approach to evidence : from “association to causation?”: applied to AS.*

There are c. 40 slides that are “hidden” on:

- The precautionary principle
- Costs (eg leaded petrol)
- Forseeability in asbestos liability cases
- Implications of complexity for innovation
- How scientists evaluate the “same” evidence differently
- Common biases within science and risk assessment
- Mechanisms of action
- Systematic review methods

Bradford Hill on object of occupational/public health

“In occupational medicine our object is usually to take action”

“Environment and Disease: Association or Causation”?

Bradford Hill. 1965,

Diversity, Complexity & Variability characterise most environment & health issues

- “diverse situations regionally”
- diverse types of environmental themes & laws”
- “case specific hazards & risks”
- *“uncertain, inconclusive, & contested science”*
- *“evolving dynamic states of scientific, technical, & economic knowledge”*
- “addressed by diverse scientific disciplines”
- “Involving *diverse stakeholders* **with** *conflicting interests & values*”
- *multi –causality*
- “requiring wise use of *7 key environmental/health principles*, including *precaution.*”

‘The Irish Potato Famine and Precaution-1846

"Are you to hesitate in averting famine which may come, because it possibly may not come?"

Is it not better to err on the side of precaution than to neglect it utterly?"

Sir Robert Peel, UK Parliament, 27 March 1846

Origins of the Precautionary Principle: German Clean Air Act 1974 & Report 1985

The **vorsorgeprinzip** (“foresight” or “precautionary principle”) is a “**principle of political action**” with elements of :

- **General reduction of environmental burdens** (limitations of the “assimilative capacity of the environment” ie **planetary boundaries**)
- Promotion of clean production & **innovation**
- **Anticipatory Research** & monitoring
- **Action** to reduce risks **before “specific hazards are encountered”**
- Costs of action not to be disproportionate to likely benefits: the **proportionality principle** now also in EU law.

An EU definition of the precautionary principle in Case law.

*“Where there is **uncertainty** as to the existence of or extent of risks to human health the institutions may take protective measures **without having to wait until the reality and seriousness of those risks become fully apparent**”*

ECJ, BSE, 1998, EEA, 2013, p649

EEA working definition of the Precautionary Principle

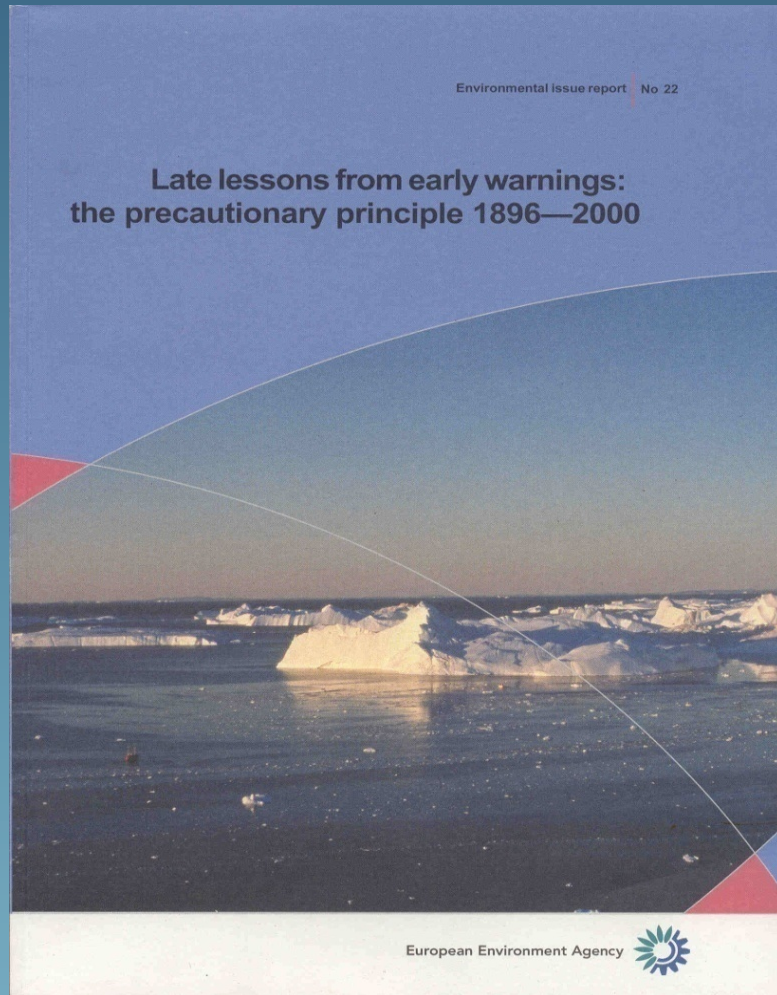
- “The PP provides **justification for public policy actions** in situations of ***scientific complexity, uncertainty and ignorance***,
- where there may be a need to act in order to avoid, or reduce, ***potentially serious or irreversible threats*** to health or the environment,
 - using ***appropriate strengths of scientific evidence***, and
 - taking into account the likely ***pros and cons of proportionate actions and inactions***”.

Gee, “More or less precaution?”, in Late Lessons, EEA, 2013.

Homo Sapiens (tragicus?) as slow learners?

Two volumes

2001



2013



European Environment Agency



34 case studies in the "Late Lessons" reports...

5 very relevant to aerotoxics syndrome= **red**

'Environmental chemicals'

- **Beryllium**
- **PCBs**
- CFCs
- TBT antifoulants
- **Mercury Minamata**
- Environmental Tobacco
- Perchloroethylene
- Booster biocides
- DBCP
- DDT
- Vinyl chloride
- Bisphenol A

Ecosystems

- Ecosystems resilience
- **Great Lakes pollution**
- Fish stock collapse
- Acid rain
- **Bee decline, France**
- Invasive alien species
- Floods
- Climate change

Transport fuel additives

- Benzene
- MBTE
- **Leaded petrol**

'Micro technologies'

- Nano
- GMOs & Agro-ecology

Animal feed additives

- **BSE, 'mad cow disease'**
- Beef hormones
- Antibiotics

- Asbestos

Pharmaceuticals

- **Contraceptive pill**
- DES

Radiations

- X-rays
- **Mobile phones**
- **Nuclear accidents**



Use of Precaution in 6 of the 34 “Late Lessons” case studies

- France: TBT 1984; “Gaucho” 1999: and some uses of BPA, 2014
- EU : antibiotics in animal feed; hormones in beef; and 3 neonicotinoid pesticides, 2013
- EU: the PP “frames” REACH, Pesticides, & GMOs regs: and a voluntary code of practice for nano.

“Useful truths” that can take years to be generally received.

*“You will see by it, that the Opinion of this **mischievous Effect from Lead is at least 60 years old**; and you will observe with concern **how long a useful truth may be known and exist, before it is generally received and practiced on**”.*

Benjamin Franklin, 1818. See “Lead in petrol makes the mind give way”, Late Lessons from Early Warnings, EEA, 2013..

The “authoritative but unsubstantiated
assertion of safety”: **Leaded petrol: the
“gift from god”** (G.Motors)

*“We have given this “very serious
consideration..**although no actual
experimental data has been taken”..***

...we are confident that ***“the average street
will probably be so free from lead that it
will be impossible to detect it or its
absorption”***

General Motors reply to US Surgeon General
querying safety of leaded petrol, **1925**.

The early warning on Leaded petrol at the one day “trial” of leaded petrol, May

1925

“the development of lead poisoning will come on so insidiously ..that leaded petrol will be in nearly universal use..before the public and the government awakens to the situation.”

Yendell Henderson, Professor of Physiology at Yale.

“Lead makes the mind give way: lead in petrol”

Needleman & Gee, Late Lessons, EEA 2013

Costs of Leaded petrol 2013

- **Multi biological impacts** in children and adults with no safe level (EFSA 2010)
- Costs mainly from **lost lifetime productivity from reduced IQ in children-**
- Current estimate is **1.5 Euro per gram of lead/litre** in urban areas from petrol
- Giving annual costs of **4-6% GDP** over the leaded years.

See “Costs of inaction” Skou Andersen and Clubb; EEA, 2013.

CFCs and “global experimentation”

“..neither governments nor multinational companies have a mandate for global experiments.....”

....CFCs provide a stark warning..

...all too often technology outstrips the science needed to assess the risks..

*...Policymakers must learn to recognise **when ignorance has been replaced by understanding, however rudimentary**”*

Joe Farman, Halocarbons and the ozone “hole”, Late Lessons from early warnings”, 2001.

Research **eventually** shows that the **Nature of Harm** expands over time....

- **Asbestos:** 1929 asbestosis; 1954 lung cancer; 1959 mesothelioma, 2012 throat & other cancers
- **Tobacco:** 1951 lung cancer; 2012 many cancers, foetal harm; heart disease
- **PCBs:** 1960s bird reproduction; 2012s neurological harm in children; soil contamination
- **Lead:** 1979 brain damage in children; 2012 heart disease in adults
- **Mercury:** 1950 brain damage & neurological; 1960s birth defects 1990s childrens IQ & behavioural
- **DES:** 1970 vaginal cancer; 1980s lifelong reproductive problems; 2013 breast cancer; 2015 grandchildren's reproductive harm.

.....and **Exposures** expand over time.....

- **Asbestos/DBCP/Be producers, users, bystanders** eg insulators, plantation workers, passive smokers
- **Domestic:** **asbestos** mesothelioma deaths from washing overalls; children of asbestos workers; **smokers** families
- **Environmental:** near asbestos & **lead** mines and factories; teachers from asbestos; **DBCP** in water; tobacco; **PCBs**;
- **Consumers:** BPA; nano;
- **Next generations:** Asbestos, **radiations**, **Mercury**, DES, **climate changes**
- **Target to non target species:****neonicotinoids** & Bees; Polar bears & fish from PCBs; oysters from **TBT**; fish from **the Pill**

And harm is caused at lower & lower levels of exposure...

- Asbestos
- Lead
- PCBs
- Mercury
- TBT
- Radiations
- BPA....etc

....often with, eventually, no known threshold...

eg Lead (EFSA, 2012).

- *“safe” limits always come down.....with very few exceptions*

See “Late Lessons from Early Warnings”, EEA, 2001,2013.

“Why do Businesses not react with precaution to early warnings?”*

- ***Costs of harm are externalised onto victims & societies***
- Predominant business model is to **maximise economic value to shareholders**: “Sole responsibility of a company is to increase its profits so long as it stays within the rules of the game” (Friedman,1970)
- **Fear of litigation**
- Scientific uncertainty
- **Weak and “captured “ regulatory agencies**
- **Psychological barriers** eg coping with low probability, high impact events; “self serving bias”, “**willful blindness**”, personal/professional **values conflicts**

(* See “Late Lessons” chapter, Le Menestrel et al, EEA ,2013

UK Court of Appeal on **foreseeability** of “unknown harm”

*“Liability would arise where the applicant **should reasonably have foreseen a risk of some pulmonary injury, not necessarily mesothelioma**”*

***Exposure to the worker had ceased before asbestos induced mesothelioma was established** in 1959/60*

(Asbestosis & lung cancer were “established” in 1929 and 1955)

(1996 case. See **panel by Owen McIntyre**, in “**Protecting early warners & late victims**” Carl Cranor, EEA, **Late Lessons**, 2013_

“Manufacturing Scientific Doubt”

“Doubt is our product since it is the best means of competing with the ‘body of fact’ that exists in the mind of the general public.”

From an executive at Brown & Williamson, Tobacco Company, 1969.

See EEA chapters on Beryllium, tobacco, leaded petrol, climate change etc.

And Michaels 2009: Oreskes, 2010 on manufacturing doubt.

Something light Cornered

by Mike Baldwin

10-7 © 2013 Mike Baldwin/Dist. by Universal Uclick www.cornered.com
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Baldwin



“What’s important is that we learn from what we must never admit happened.”

Health v Power?

*“I have become aware that in investigating the environmental health impact of large industries, especially if they have military interests, **we are confronting the seat of immense economic and political power.***

Doctors constitute no more than an innocent and ill-equipped David confronting Goliath, the well-armed and experienced giant.”

Rose G.A. 1991, *Environmental Health Problems and prospects*. Journal, Royal College of Physicians, 25: 48 – 52.

Cited in Alice Stewart 1991. Evaluation of delayed effects of ionising radiation: a historical perspective. Greenberg, M Am Journal Industrial Medicine. 20: 805 – 810.

“Seattle: we have a problem”

First Plausible early warning about AS- 1953

“The observations of the flight crews constitute the **first evidence of the existence of the problem.**

They have repeatedly reported presence of smoke and odour in the occupied compartments of the airplane”

Boeing, Decontamination Program, dec 18 1953.

“there must be something there” 2000

*There is absolutely **no doubt in our minds** that there is a general health issue here.....*

*With the **weight of human evidence and suffering** which is quite clear, **there must be something there”***

BAe Systems, Australian Senate Inquiry on AS, 2000.

email from George Bates, Boeing Environmental Controls, 26 October 2007

- “...*the Propulsion folks do not account or certify the bleed air quality ..*
- *Klym was the most recent to try to get the Propulsion folks to step up to owning their system by-products....*
- *GE and RR engine specs do not mention bleed air quality when it comes to CO/CO2 or hydrocarbon by-products....*
- *With all diversions (about one every two weeks) and return-to-base events due to haze in the cabin, (from failed fan and forward IPC bearing oil seals allowing oil by-products)..*
- *I would have thought the FAA would have made the engine manufacturers address this by now”.*

“Waiting for Tombstones”?

“Bottom line is, I think we are looking for a tombstone before anyone with any horsepower is going to take interest.”

26 October 2007 email from George Bates, Boeing Environmental Controls

You are not alone with your AS problem.....

Some (28) similarities between **Aerotoxic Syndrome** & other Hazards in *“Late Lessons from Early Warnings”*

- The bleed air **innovation** was a *“fortuitous discovery”* (Antibiotics as growth promoters)
- Innovation needed to deal with high compression engines & **saved fuel & money** (Pb petrol)
- **Military origins** (Berryllium/nuclear)
- **Very early warnings-1953/5 for AS** (all LLEW cases: eg 1897/8 for climate change ,asbestos, benzene)
- Harassed “early warning” scientists? (Galileo; George Baker; Dr Stockman; Prof Needleman/Pb; Stewart & Mancuso/radiation)

Similarities.....

- Single to mixtures of hazardous substances (tobacco smoke, welding fumes, hot rubber fumes)
- Many isomers (PCBs)
- breakdown products a/o isomers more toxic than parent chemical (Dioxins, PCBs)
- Acute to chronic effects (all health; & bees cases)
- Misunderstood/misapplied Occupational Exposure Limits (asbestos, radiation, PCBs, Be)
- Inappropriate generalisations being misapplied to “*unique environment of aircraft*” (Bees, lead)

Similarities.....

- No routine monitoring of relevant toxins (PCBs, bees/neonics)
- Unreliability of odour threshold (VCM)
- Limited research monitoring/health studies during contamination incidents (DBCP, PCBs)
- No *timely* long term health studies of crew & publics (DES,DBCP)
- Much variability in sensitivities in exposed groups (all health cases)
- Limited animal studies of relevant toxins (PCBs, Bees,)
- “No evidence of harm” misinterpreted as “evidence of no harm” (all cases)
- Argumentation against hazards: “no convincing evidence of harm”(all)
- Unsubstantiated assertions/assumptions (Fukushima, Pb, bees)

Similarities.....

- Language imprecision: not “toxics” but “irritants “,”odours” (Pb:“*normal*” & *natural*” levels; “inert” dusts)
- “Funding bias” in research (asbestos, Pb, tobacco, RF, BPA, pharma)
- Large economic/political pressure to deny hazard (all cases)
- Inappropriate/deficient regs & “light touch” regulation (most cases)
- Probable gaps/conflicts in regulatory oversight (BSE/Food, Fukushima)
- Industries shun conferences that they do not control? (most cases)
- Highly motivated victims can become “experts” (Tait/asbestos; beekeepers)
- “How long a useful truth may be known..before it is generally received and practiced on”.(Ben Franklin on leaded paint: 1818!)

Some Implications of complexity for innovation....

- Expect **“surprises” & unintended consequences***
- Avoid **technological lock in and pathway dependence**
- Promote **“midstream modulation”** of innovation pathways
- “Promote **diverse, robust, adaptable, technologies**” (EEA LLEW,2001)
- Promote **responsible research & innovation for social purposes** (EEA LLEW,2013)
- **With public engagement in helping to choose strategic innovation pathways to 2050** eg on food, energy, transport.

** See “Science on the Verge”, Benessia, Funtovicz, Saltelli, Giampetro et al 2016*

“Surprise comes to the prepared mind”

Pasteur

(See CFCs & Ozone “hole” chapter for impact of “unprepared” USA minds on not seeing the “hole” via their satellites, *Late Lessons from Early Warnings*, vol 1, EEA, 2001)

“Ban the boxes, consider continuums”

- “nature **and** nurture” as causes of IQ, ill health, etc
- “subjective **and** objective” (physics)
- acute **and** chronic ill health
- ***Disease progression***
- ***Single to multi-causality***
- association **and** causation in environmental health
- ***From low to strong “strengths of evidence” for different purposes***

Multi-Step

The Complex Disease Process.

PREPARATION

INITIATION

PROMOTION

RETARDATION

PROGRESSION

DISEASE:

-SEVERITY

-PREVALENCE

WITH **MULTIPLE CAUSES**; SEVERAL **PATHWAYS**;
AND EFFECT OF **GENETICS, DOSE, TIMING, & HOST
STATE**

Unravelling the gene/environment interactions..?

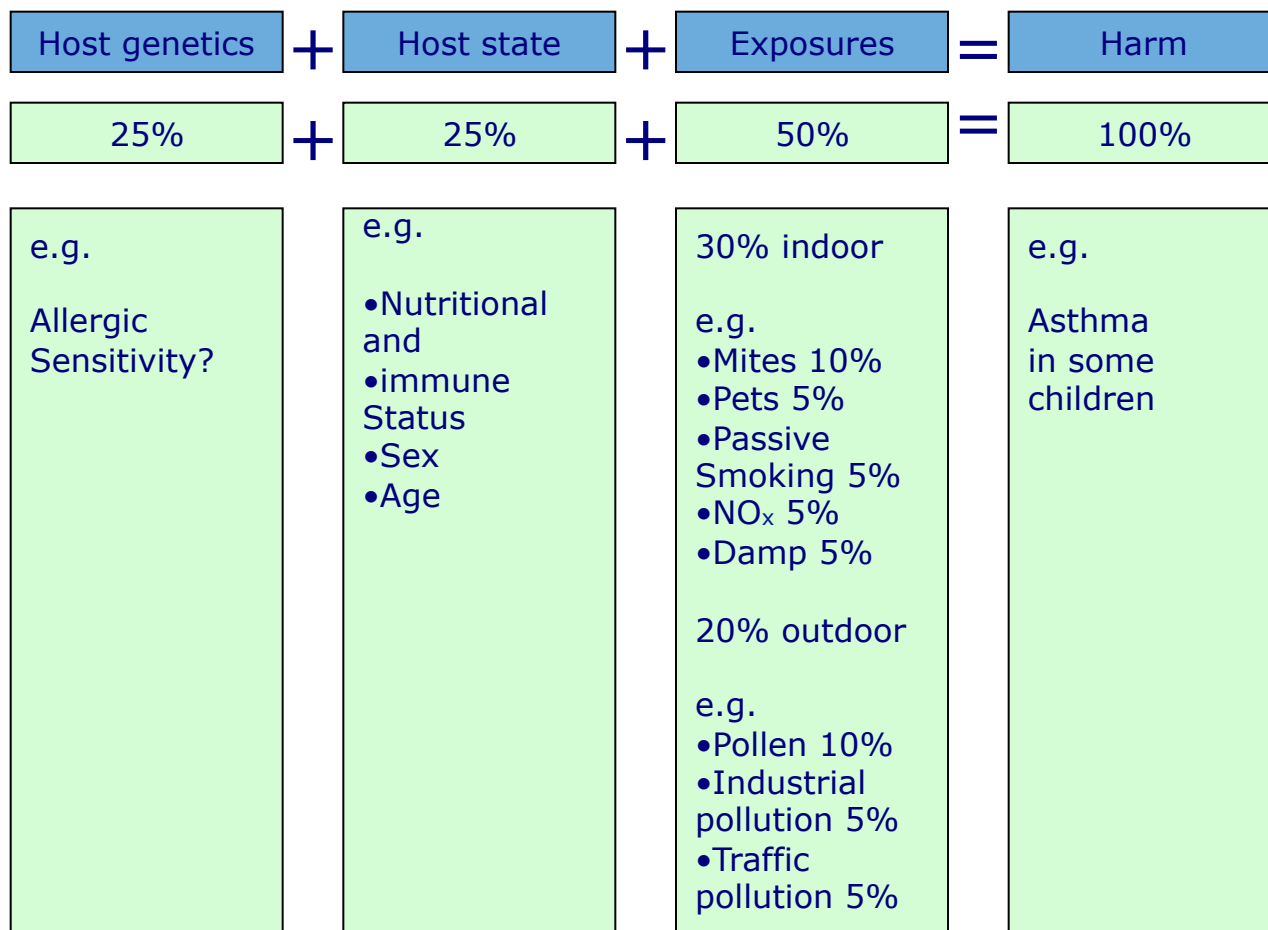
“Toxicogenomics combines:

- *genetics*
- *transcriptomics (mRNA)*
- *metabonomics*
- *bioinformatics*

..with conventional toxicology in an effort to understand the role of gene/ gene & protein expression/environment interactions in disease”

Nat. Centre Toxicogenomics/NIEHs, USA, “Phenotypic anchoring: linking cause and effect” EHP, May 2003.

Illustrations of **multi-causality** in childhood asthma



% are illustrative only. EEA, 1999

Bees & Gaucho: search for the **single cause**..of all impacts.. in all regions... ?!

*“The Risk Assessment **does not allow us to demonstrate** that maize seed dressing with Gaucho can be **solely responsible**, at **national level**, for **all colony losses, behavioural troubles, honey bee mortalities, or general decline in honey production**”*

French Commission for Toxic Products , 2002:
see “Seed dressing systemic insecticides and honeybees”, Maxim L. & van der Sluijs,J., Late Lessons from Early Warnings, EEA, 2013.

or embrace **multi-causality**....?

*“Gaucho...is of concern (on maize) as **one of the explanatory elements for the weakening of the bee populations** observed despite the ban of Gaucho in sunflowers.”*

Multifactor study of the Honeybee Colonies Decline, French Scientific & Technical Committee, 2003, see Late Lessons, Bees chapter

Bradford Hill's Illustrative Strengths of Evidence for Action..

- ***“relatively slight evidence”*** for banning a morning sickness pill
- ***“fair evidence”*** for reducing/eliminating exposure to a probable carcinogenic oil at work
- ***“Very strong evidence”*** before we made people burn a fuel in their homes that they do not like or stop smoking the cigarettes and eating the fats and sugar that they do like”.

Some different **Strengths of Scientific Evidence** for association and causation....

- **“Beyond all reasonable doubt”** (“established” scientific causality & criminal law)
- **“Reasonable certainty”** (Int.Panel Climate Change , 2007)
- **“Probable”** carcinogen (International Agency Research Cancer)
- **“Balance of probabilities/evidence”** (IPCC,2001; civil law)
- **“Possible** carcinogen (IARC)
- **“Reasonable grounds for concern”** (EU Communication on PP)
- **Credible evidence to suspect a link”** (Coroner, Westgate)
- **“Scientific suspicion of risk”** (Swedish Chemicals Law, 1975)

The “appropriate “strength of evidence for precautionary action is an **Ethical choice**.

*Who benefits, and who gains, **from being wrong in acting, or not acting**, early enough to prevent harm?*

- Short term, specific, **economic interests**?
- Or the longer term **health & wellbeing** of people and their environments?

What do the **Military** share with Communities managing
Infectious diseases and Occupational/
environmental/ecosystems health?

*“They Act on incomplete evidence
to Avoid Defeat or Harm”*

(ie the *“precautionary principle”*; which is in c 60
International Agreements; & the EU Treaty)

An HSE view of the AS evidence..2017

*“**We can see nothing** in this most recent or previous evidence that provides **clear and consistent evidence** of causal long term health effects”.*

Simon Clarke HSE On Aerotoxic Syndrome), 13 September 2017

Expect inconsistency from variability

"Consistency in nature does not require that all, or even a majority of studies find the same effect."

"If all studies of lead showed the same relationship between variables, one would be startled, perhaps justifiably suspicious"

Needlemann (1995) "Making Models of Real World events: the use and abuse of inference, Neurotoxicology and Teratology, vol 17, no. 3.

"No two chemicals produce exactly the same pattern of hepatotoxicity"

NCT/NIEHS, Richard Paules, EHP, May ,2003

“No evidence of Harm” is not the same as
“evidence of no harm”.....

...because **no/little relevant, reliable, long term** research
is available,

..or because of the limitations on what *could* be known
with existing scientific methods, under **complexity and
multi-causality**.

*How do scientists evaluate the
“same” evidence differently?*

Different Conclusions from “Same” Knowledge Evaluated

Classification of **TCE** risk assessment reports in 1995/6
(Ruden 2002)

<div>---</div> <div>Negative</div>	<div>+ - -</div> <div>Positive animal</div>	<div>+ - +</div> <div>Positive animal, negative human, plausible risk</div>	<div>+++</div> <div>Positive animal & human, plausible risk</div>
<div>1996</div> <div>ACGIH</div>	<div>1996</div> <div>HSIA, Online, Industry</div>	<div>1996</div> <div>OECD/EU UK, Int.Org.</div>	<div>1995</div> <div>IARC</div>
			<div>1996</div> <div>Deutsche Forschungsgemeinschaft, DFG, Germany</div>
			<div>1996</div> <div>MAK Germany Occ. Agency</div>

JRC/IPTS Report on “*RAPs: Differences across Food Jurisdictions*”(2008)

*“When different risk assessors..reach different conclusions..they do so because they are adopting different **Risk Assessment Policies (RAPs)**.....*

*“data and documents do not interpret themselves: **interpretation often involves judgements and assumptions**” (p10)*

Some Common Biases in Research & Risk Assessment

- **Methodological biases** usually towards “false negatives” ie harmless becomes harmful
- **Intellectual bias** ie commitment to a paradigm; authored previous RA
- **Reporting biases**
- **Funding bias**: See the Vatican and its seeking of scientists who would contradict Galileo; & histories of Asbestos, Lead, some Pharma, Tobacco, BPA, & Mobile phones..**where source of funding strongly predicts nature of the results**

Intellectual Bias: the Beef Hormones case at WTO

*"The European Communities alleges that
"that Drs. Boisseau and Boobis,..as
"co-authors" of the JECFA reports, "**cannot
be considered to be independent and
impartial....***

*because this would amount to **asking them
to review and criticise reports that are
their own doing"**.*

WTO Appellate Body agreed

Source: p27, para 65 World Trade Organization, WT/DS320/AB/R, "United States-Continued Suspension of Obligations in the EC-Hormones Dispute", (16 October 2008)

IPPC advice to its scientific authors about the *perils of prevailing paradigms*

“Be aware of:

“the tendency for a group to converge on an expressed view and become over confident in it....

...Views and estimates can also become anchored on previous versions, or values, to a greater extent than is justified”.

(Guidance Note on Uncertainty to its 4th Assessment authors, Intergovernmental Panel on Climate Change, 2005/2010)

Some Intellectual “Interests & commitments” of Scientists

- From **different scientific disciplines** (toxicology v endocrinology/BPA; microbiology v ecology/GMOs)
- Prior beliefs
- **Paradigms preferred**
- Prejudices
- Passions & jealousies

(See «***Rivals: Conflict as the Fuel of Science***», M. White, Vintage, 2002, for Newton v Leibnitz, etc)

“Some Generic Sources of Divergent Evaluations of “same” evidence

- A. **Institutional/Cultural factors** eg Committee mandate & membership & Question addressed
- B **Knowledges accepted** for review
- C **Weights given** to knowledges reviewed
- D “Rules” by which knowledges assessed become evidence asserted.
- F Approaches to evaluating **Uncertainties, Understandings, Confidences, & Likelihoods** about the knowledge base and cause/effect links; and
- G “Rules” for conclusions about **Strengths of Evidence** for causality and **Strengths/nature of recommendations for action**

Source: DG draft conclusions ,EEA Workshop, 2008.

The Bradford Hill approach to association and causation

Bradford Hill: the “*decisive question*” is.....

“The ‘*cause*’ of illness may be immediate and direct,
it *may be remote and indirect*.....But...the decisive
question is;

*whether the frequency of the undesirable event B will be
influenced by a change in the environmental feature A?”*

“Environment & Disease: association or causation?”

Bradford Hill, 1965

From *observed association* to a
robust *causal inference*?

“What *aspects of that association* should we
especially consider before deciding that *the most
likely interpretation* of it is causation?”

In what circumstances *can we pass from this
observed association to a verdict of
causation?*”

Do we need to know *how* A causes B before acting to reduce A?

“How such a change exerts that influence may call for a great deal of research.

However, before deducing 'causation' and taking action we shall not invariably have to sit around awaiting the results of that research.

And “Biological plausibility depends on the knowledge of the day ...a feature of the evidence that we cannot demand”

Bradford Hill, 1965, p 295& 298.

Discovering biological “mechanisms of action” can take decades..& its absence need not weaken causal evidence

*“Yet the fact that Koch's work was to be awaited another thirty years..
(after John Snow's epidemiological observations on the conveyance of cholera by the water from the Broad Street pump)*

.. did not really weaken the epidemiological case

though it made it more difficult to establish against the criticisms of the day - both just and unjust”.

Bradford Hill, 1965, p298.

Bradford Hill on Statistical Significance

*“Too often I suspect we waste a deal of time, **we grasp the shadow and lose the substance, we weaken our capacity to interpret the data and to take reasonable decisions whatever the value of P.**”*

Hill. 1965, “*Environment and Disease: Association or Causation*”?

Bradford Hill recognised his “viewpoints” were asymmetrical

The **presence** of the “viewpoints” provides good evidence **for** causation; but
their **absence** may not provide good evidence **against** a real association.

*Eg “if specificity exists we may be able to draw conclusions without hesitation;
If it is not apparent, we are not thereby necessarily left sitting irresolutely on the fence”;*

And, on biological plausibility: an observed association “*may be new to science or medicine and must not therefore be too readily dismissed as implausible or even impossible*”.

Given what we now know about multi-causality and complexity in
biological systems, **this asymmetry is now larger than in 1965**

The 9 Bradford Hill *“features of evidence”* that help us to move from *an observed association to a robust inference of causation:*

applied to the Aerotoxics evidence

Strength of association: case studies & clinical data indicate clear health impacts in significant proportions of exposed groups

Consistency: clinical data consistent with known toxic effects of OPs; and across varying aircraft types /countries

Specificity: AS is a syndrome (like AIDs; MS; Occ. Asthma; MCS; Gulf War & Autism syndromes) –and with common neurological/respiratory symptoms; linked to oil leakage/pyrolysis products exposure.

Temporality: cabin air contamination precedes linked health effects

- **Biological gradient:** more contaminant exposure often causes greater health effects; but low dose effects also apparent suggesting non-linearity

Plausibility: known effects of OPs & other contaminants support causal link; and we *don't need specific "mechanisms of action" knowledge to act*

Coherence: animal/human data plus analogous contaminants (OPs) support causal link

Experiment: health effects often reversible after exposure cessation

Analogy: PCBs; hot rubber fumes; welding fumes; traffic fumes, occupational asthma, leaded petrol, methyl mercury, OP pesticides, tobacco smoke.

Conclusion: Strength of evidence for AS?

(A quick evaluation!)

- Overall weight of evidence **supports a causal link** between plane cabin toxics contamination and health effects.
- The link is more likely than not ie above the **“balance of probabilities”** strength of evidence
- Case control study urgently needed
- There needs to be an **independent “systematic review”** (Eg via NAS/**SYRINA methods**) of the current AS evidence
- Try a **Frequent Flyers Citizens Jury** ?
- Meanwhile: action should be taken to
 - **monitor AQ & remove the hazard** and
 - **compensate the victims via a no fault scheme??**

(cf British Nuclear Fuels radiation compensation scheme 1985-ongoing)

Air Pollution and Autism Spectrum Disorder: a similar strength of evidence for causation?

“Given the general consistency of findings across studies, and the exposure window specific associations recently reported, the overall evidence for a causal association between air pollution and ASD is increasingly compelling”.

Air Pollution and Autism Spectrum Disorders: Causal or Confounded?
Weiskopf et al Curr. Envir. Health Rpt. (2015) 2:430–439

Systematic Reviews can increase confidence in evidence evaluation...

By using **transparent and reproducible methods** of evidence evaluation that acknowledge uncertainties, variabilities, and ignorance.....

See SR methods in GRADE; Navigation Guide; OHAT Guide; **NAS Guide, & SYRINA for EDCs....**

Guides on **Systematic Review** methods: for Endocrine Disrupting Chemicals

“Application of Systematic Review Methods in an overall strategy for Evaluating low dose toxicity from endocrine Active Substances”

NAS, USA, 2017

“A proposed framework for the systematic review and integrated assessment (SYRINA) of endocrine disrupting chemicals”

Vandenberg et al , Env Health, 2016.

“Bradford Hill’s” Case for Action”

“All scientific work is incomplete..

..that does not confer on us the freedom to ignore the knowledge we already have or to postpone the action that it appears to demand at the given time”

“Environment & Disease: association or causation?” (Bradford Hill, 1965, p 300)

Avoid “paralysis by analysis”!

USA Action: “Research hazard removal; monitor air quality; report in a year”

“The technology ..shall have the capacity, at a minimum:

(1) to remove oil-based contaminants from the bleed air supplied to the passenger cabin and flight deck; and

(2) to detect and record oil-based contaminants in the portion of the total air supplied to the passenger cabin and flight deck from bleed air.

“Not later than 1 year.... the Administrator shall submit....a report on the results of the research and development work.

H.R. 658, USA Congress, February 14, 2012

Monitoring Cabin air quality is feasible

*“There are **commercially available air quality sensors**....including – catalytic-bead sensors, metal-oxide semiconductor sensors, electrochemical sensors... wireless sensor networks*

A prototype of such a system has been successfully demonstrated in a Boeing 767 mock-up cabin”

USA FAA report, 2013

Towards “Responsible Innovation”.....?

*“We aim to “ to articulate and explore four **integrated dimensions of responsible innovation: anticipation, reflexivity, inclusion and responsiveness.** Although this frame-work for responsible innovation was **designed for use by the UK Research Councils, and the scientific communities** they support, we argue that it has more general application and relevance”.*

*“**Developing a framework for responsible innovation**” Jack Stilgoe, Richard Owen, Phil Macnaughten, Research Policy, 2013.*

See also **panel on responsible research & innovation**, R von Schonberg, in *“**More or less precaution?**”, p 660-662, “Late Lessons”, 2013.*

Thank you

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All Late Lessons chapters from both vols of “Late Lessons” (2001,2013) are available from the EEA website as PDFs

And as a Kindle for vol 2