Risk assessment - uses,limitations and abuses

Dr. C. Vyvyan Howard. FRCPath.

c.v.howard@liv.ac.uk

Legacy: ethical problems of stewardship

Vyvyan Howard

c.v.howard@liv.ac.uk

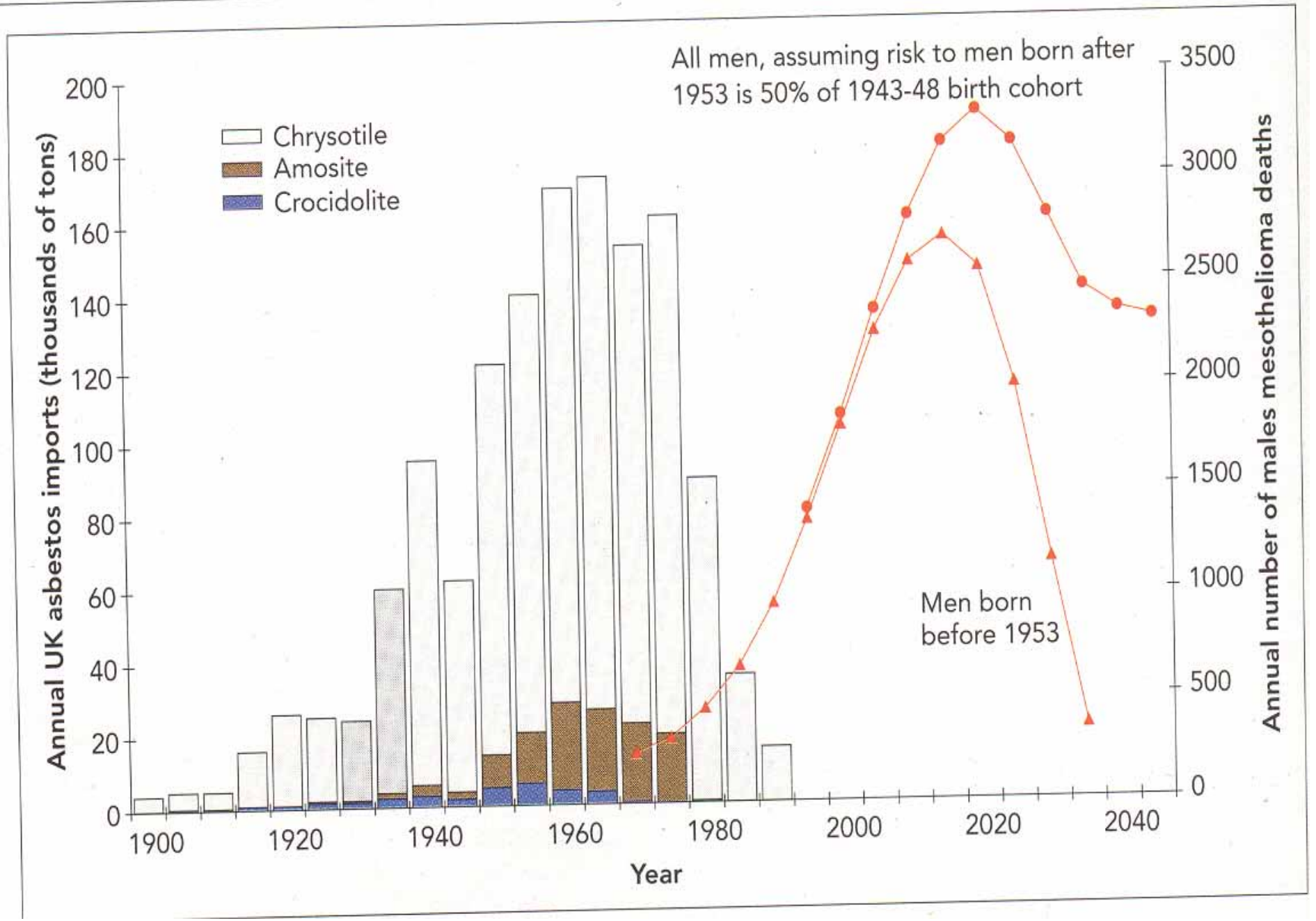
Ethical problem

- - Do we have a duty of care to the, yet unborn, children of future generations?
- - If yes, then should we have ethical review of research and development being conducted by industries, governments etc?
- - If activities are ‘pervasive’, i.e. they impinge directly upon our lives, should developers have societal ‘permission’ BEFORE they start work?

"The discoverer of an art is not the best judge of the good or harm which will accrue to those who practice it."

Plato, *Phaedrus*

UK asbestos imports and predicted mesothelioma deaths



Environmental issue report No 22

Late lessons from early warnings: the precautionary principle 1896—2000

European Environment Agency

ISBN 92-9167-323-4

1898	UK Factory Inspector Lucy Deane warns of harmful and 'evil' effects of asbestos dust
1906	French factory report of 50 deaths in female asbestos textile workers and recommendation of controls
1911	'Reasonable grounds' for suspicion, from experiments with rats, that asbestos dust is harmful
1911 and 1917	UK Factory Department finds insufficient evidence to justify further actions
1918	US insurers refuse cover to asbestos workers due to assumptions about injurious conditions in the industry
1930	UK Merewether Report finds 66 % of long-term workers in Rochdale factory with asbestosis
1931	UK Asbestos Regulations specify dust control in manufacturing only and compensation for asbestosis, but this is poorly implemented
1935–49	Lung cancer cases reported in asbestos manufacturing workers
1955	Doll establishes high lung cancer risk in Rochdale asbestos workers
1959–60	Mesothelioma cancer in workers and public identified in South Africa
1962/64	Mesothelioma cancer identified in asbestos workers, in neighbourhood 'bystanders' and in relatives, in the United Kingdom and the United States, amongst others
1969	UK Asbestos Regulations improve controls, but ignore users and cancers
1982-9	UK media, trade union and other pressure provokes tightening of asbestos controls on users and producers, and stimulates substitutes.
1998–99	EU and France ban all forms of asbestos
2000–01	WTO upholds EU/French bans against Canadian appeal

Radiation: early warnings and actions

1896	Injuries from exposure to X-rays noted by Edison, Tesla and Grubbe.
1899	John Dennis, New York journalist, campaigns for licensing of radiologists and warns of harm from X-rays.
1904	Death of Edison's assistant from complications arising from severe X-ray radiodermatitis.
1904	William Rollins, Harvard dentist/doctor, publishes many warnings on X-ray hazards, and recommendations on prevention for radiologists and patients, including pregnant women.
1913	First published rules of voluntary radiological protection by German Radiological Society.
1924	New York dentist, Theodore Blum, identifies 'radium jaw' in radium dial painters: but wrongly attributes this to phosphorous.
1925–29	Harrison Martland, New Jersey pathologist, identifies radium as the cause of the jawbone cancers in the dial painters studied.
1928	Establishment of the International X-ray and Radium Protection Committee: which later became the International Committee on Radiological Protection (ICRP).
1934	Reports by Colwell and Russ, on the death of more than 200 radiologists from radiation-induced cancers.
1949	ICRP concludes that there is no dose threshold for radiation-induced cancer and optimisation of all exposures is crucial.
1958	Alice Stewart reports that 'low dose' X-rays to pregnant women can cause leukaemia in their children. Not generally accepted until the 1970s.
1961	UK publishes regulations covering the use of radioactive substances.
1977	ICRP updates its radiation protection recommendations and links dose limits to risk.
1988	Regulations covering radiation doses to patients produced in the UK
1990–97	NRPB reports 20 % of medical X-rays are probably clinically unhelpful; that 50 % of the collective dose to patients could be avoided; and that individual doses for the same X-ray vary by 100x between hospitals.
1990	ICRP concludes in Publication 60 that the risk of radiation-induced cancer is 4-5 times greater than estimated in 1977 — reduces the occupational dose limit to 20mSv per year.
1996	EU Directive on Ionising Radiations based on ICRP 60 which will be mandatory on member states.

1907	Laboratory experiments by Weigert on the decomposition of ozone photosensitised by chlorine
1934	*Ditto* by Norrish and Neville
1973	Global survey of CFCs by Lovelock *et al.* showing their distribution in the atmosphere worldwide
1974	Molina and Rowland publish their theoretical arguments that CFCs would be destroying the ozone layer
1977	United States bans CFCs in aerosols based on 'reasonable expectation' of damage, followed by Canada, Norway and Sweden.
1977	Research-oriented 'world plan of action on the ozone layer' agreed, overseen by UNEP
1980	European decision restricting use of CFCs in aerosols, but rising use in refrigerators, etc. marginalises this restriction
1985	UNEP Vienna Convention for the protection of the ozone layer agrees research, monitoring, information exchange and restrictions if and when justified
1985	Farman, Gardiner and Shanklin publish results showing hole in ozone layer over Antartica
1987	Montreal Protocol on protection of the ozone layer is signed, with phasing out of ozone depleting substances for both developed and developing countries within different timescales
1990s	Increasing finance to developing countries to help them reduce their dependence on ozone depleting substances
1997	Amendments to the Montreal Protocol in order to restore levels of chlorine by 2050–60
1999	Beijing Declaration calling for efforts to stop illegal trade in ozone depleting substances

1899	Chloracne identified in workers in chlorinated organic industry
1929	Mass production of PCBs for commercial use begins
1936	More workers affected by chloracne and liver damage
1937	Chloracne and liver damage observed in experiments with rats. Results did not gain attention from policy-makers but both labour regulators and manufacturers were made aware of the concerns surrounding PCBs
1966	Jensen discovers unknown molecules in sea eagles in Sweden — only in 1969 was he able to demonstrate that they were PCBs
1968	Poisoning of 1 800 people who had ingested PCB-contaminated rice oil in Japan gives rise to a new Japanese word: Yusho — rice oil disease, and to the first well-publicised warning that PCBs are harmful to humans
1970s	High levels of PCBs found in infertile seals of three different species
1972	Sweden bans 'open' uses of PCBs
1976	Toxic Substances Control Act (United States) — PCBs to be used only in a 'totally enclosed manner'
1979	2 000 people again poisoned, in Taiwan, by polluted rice oil. Follow-up research showed that 25 % of children born of poisoned mothers died before the age of four years
1980s	Evidence of PCB contamination of breast milk
1990s	PCBs associated with IQ and brain effects in children exposed *in utero* to mothers' PCB-contaminated diets. Fetotoxicity represents a new paradigm for toxicology
1996	EU directive to eliminate PCBs, with phase-out by 2010
1999	Chicken food contaminated with PCBs is found in Belgium

Formal Risk Assessment is a relatively recent development

- Society has belatedly ‘reacted’ to disasters in the past, rather than anticipating harm.
- Pollution of the planet with POPs and climate change are good 20th C examples
- Of course the ability of the human race to alter and/or despoil the planet is not new – the Sahara Desert is a case in point

It is clear that a mode shift was required

- Simply reacting to disasters was seen to be an inadequate approach
- Man was clearly capable of causing changes to the environment and health on a global scale
- There was a desire to adopt an anticipatory mode to try to avoid failures by using past experience to predict likely areas of hazard
- The options available are:
  - Hazard assessment
  - Risk assessment
  - Precaution

The Precautionary Principle

- "*When an activity raises threats of harm to human health or the environment, precautionary measures should be taken, even if some cause and effect relationships are not fully established scientifically*"
  'Wingspread Statement on Chemically-Induced Alterations to immune system.' Environmental Health Perspectives, 104:4, August 1996.

Precautionary principle stifles discovery

Sir—The so-called 'precautionary principle' (PP) has gained currency in discussions about environmental protection and genetic manipulation, but it should be treated with caution.

The principle has been endorsed in international treaties, including the consolidated version of the treaty establishing the European Union. In many of these documents the PP has not been explicitly defined, but the Wingspread conference attempted to define it[1]. We believe the following definition would be accepted by most proponents:

"When an activity raises threats of serious or irreversible harm to human health or the environment, precautionary measures that prevent the possibility of harm (for example, moratorium, prohibition) shall be taken even if the causal link between the activity and the possible harm has not been proven or the causal link is weak and the harm is unlikely to occur."

In our view, there are problems with the PP as so defined. The PP tells us to balance evidence in a specific way. The weight given to evidence is ordinarily thought to be a function of its epistemic warrant (the degree to which we have reasons for believing the evidence). The PP instructs us to change this normal balancing by giving evidence pointing in one direction more importance than evidence pointing in the other direction, even in cases where the evidence has the same epistemic warrant. Such discounting will distort our beliefs about the world, and will lead us to hold false beliefs. The PP cannot therefore be a valid principle for evaluating evidence.

As a principle of rational choice, the PP will leave us paralysed. In the case of genetically modified (GM) plants, for example, the greatest uncertainty about their possible harmfulness existed before anybody had yet produced one. The PP would have instructed us not to proceed any further, and the data to show whether there are real risks would never have been produced. The same is true for every subsequent step in the process of introducing GM plants. The PP will tell us not to proceed, because there is some threat of harm that cannot be conclusively ruled out, based on evidence from the preceding step. The PP will block the development of any technology if there is the slightest theoretical possibility of harm. So it cannot be a valid rule for rational decisions.

This fatal weakness of the PP illustrates a common problem in attempting to convert moral choices into legislation. The temptation is great to try to find one absolute and easily applicable principle, but such a principle will often be simplistic and will, when applied, lead to unjustifiable conclusions. Many moral choices are complex, and in making political decisions we should not lose sight of this complexity.

Søren Holm, John Harris

Institute of Medicine, Law and Bioethics, University of Manchester, Manchester M13 9PL, UK

1. http://www.wajones.org/wingcons.html

Nature **400**; 398, 1999

Sensible precautions make good science...

Sir— Søren Hòlm and John Harris strongly criticize the precautionary principle but they seem not to understand it (*Nature* **400**, 398; 1999). They complain that it is not valid for evaluating evidence, when that is not what it is for. It is a tool for decision-making, and, like many such tools, deals in expectations rather than probabilities.

The point is that it requires us to take into account not just the probability that a technology will be hazardous, but also the benefits if it succeeds and the costs if things go wrong. There may have been a very small probability that a large ship travelling at high speed in the North Atlantic would hit an iceberg, but the captain of the *Titanic* should have thought more about what could happen if it did — and all the more so because it didn't really matter if the voyage lasted a few hours more.

Holm and Harris argue that the precautionary principle would have stopped us developing genetically modified organisms (GMOs) because the greatest uncertainty about their possible harmfulness existed before anybody had produced one. But the principle does not demand that we halt research if we cannot be certain the end result will be safe (though common sense suggests it is unwise to make large investments if the end result is likely to be dangerous). It is to be applied at each stage in the process, weighing the risks in going one step further against the likely benefits if the project is successful.

That is why we and many others are arguing not for a complete ban on research into GMOs but for a five-year moratorium on field trials and commercial planting. There is a lot more research to be carried out in the relative safety of a closed laboratory first. This is always good practice, but it is especially important in the case of GMOs because of the irreversibility that is inherent in the technology. If a new drug proves to be harmful we can withdraw it, but once genes have left the laboratory there is no calling them back. The experiments in which GM milkweed was found to harm the monarch butterfly were performed in contained conditions; had this been discovered in field trials, the gene might already be spreading through the environment.

Our objection to the current field trials of GM crops is based not on whether commercial planting would be safe (though we are concerned about that), but on whether the trials themselves are safe — and whether they are well enough designed to be worth the risk. Neither has been shown to be the case. At the end of a moratorium, a much better-informed risk assessment should be possible.

C. Vyvyan Howard*, Peter T. Saunders†
**Department of Fetal & Infant Toxico-Pathology, University of Liverpool, Liverpool L69 7ZA, UK*
†Department of Mathematics, King's College, London WC2R 2LS, UK

correspondence

Risk Assessment

- The main tool used to stop the implementation of the Precautionary Principle
- Deployed as ‘proof’ that technologies are safe
- Usually presented as hard science, despite the use of unrealistic assumptions on many occasions. These assumptions are usually not explicitly stated and tend to be hidden in the text.

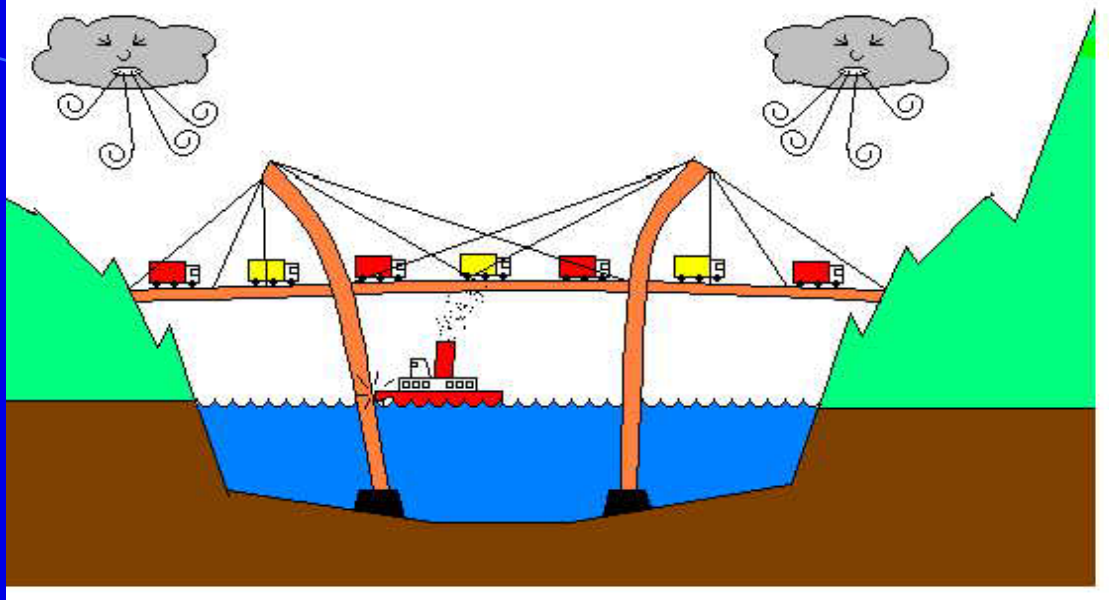
Risk Assessment – 4 phases

- **Hazard identification** – requires insight and understanding of the system in question
- **Hazard assessment** – costs time and money for hard science – positive findings require action
- **Exposure assessment** – can be very expensive and, for human exposure, complex
- **Risk assessment** – depends totally on the 1st three steps

Risk Assessment – Invented by Engineers

- Used to assess the integrity of structures
- Most information required is available
- Realistic risk assessments possible
- Lead to over design of structures
  - Bridges and buildings typically x 5
  - Aircraft typically x 1.1 to 1.2

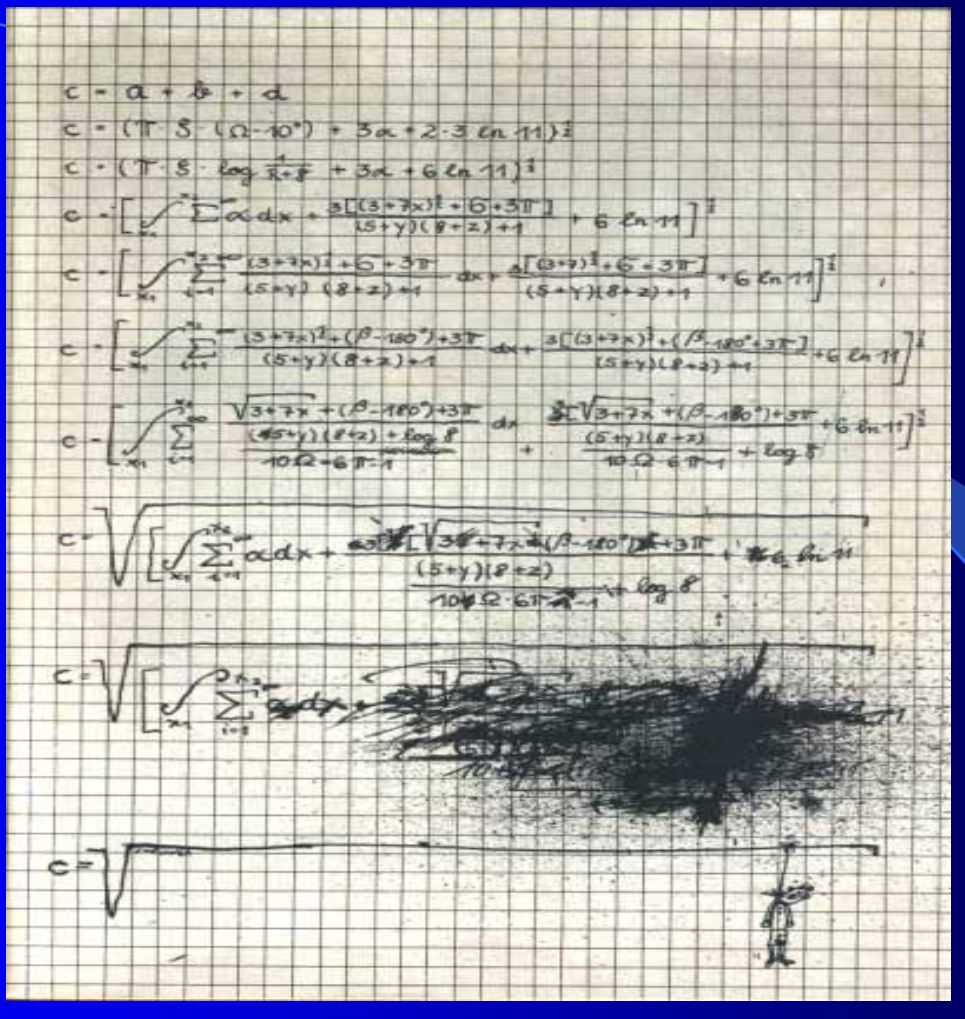
  The tighter the margin – more research required



Risk assessment was designed by engineers to assess the reliability of engineered structures, where most of the facts are known or can be measured.

Risk assessment in engineering is not foolproof

- Despite sophisticated models based on hard data and years of experience unpredictable events still happen
- This represents either a failure of hazard identification or of hazard assessment



Soooo - Mathematical models can be problematic

Complex Systems

- Risk assessment is now being applied to very complex systems - such as ecosystems
- It is impossible to have comprehensive hazard data for such systems
- Missing data is often provided by ‘data models’, but these can be subjective
- Sometimes the whole risk assessment can be based solely upon data models

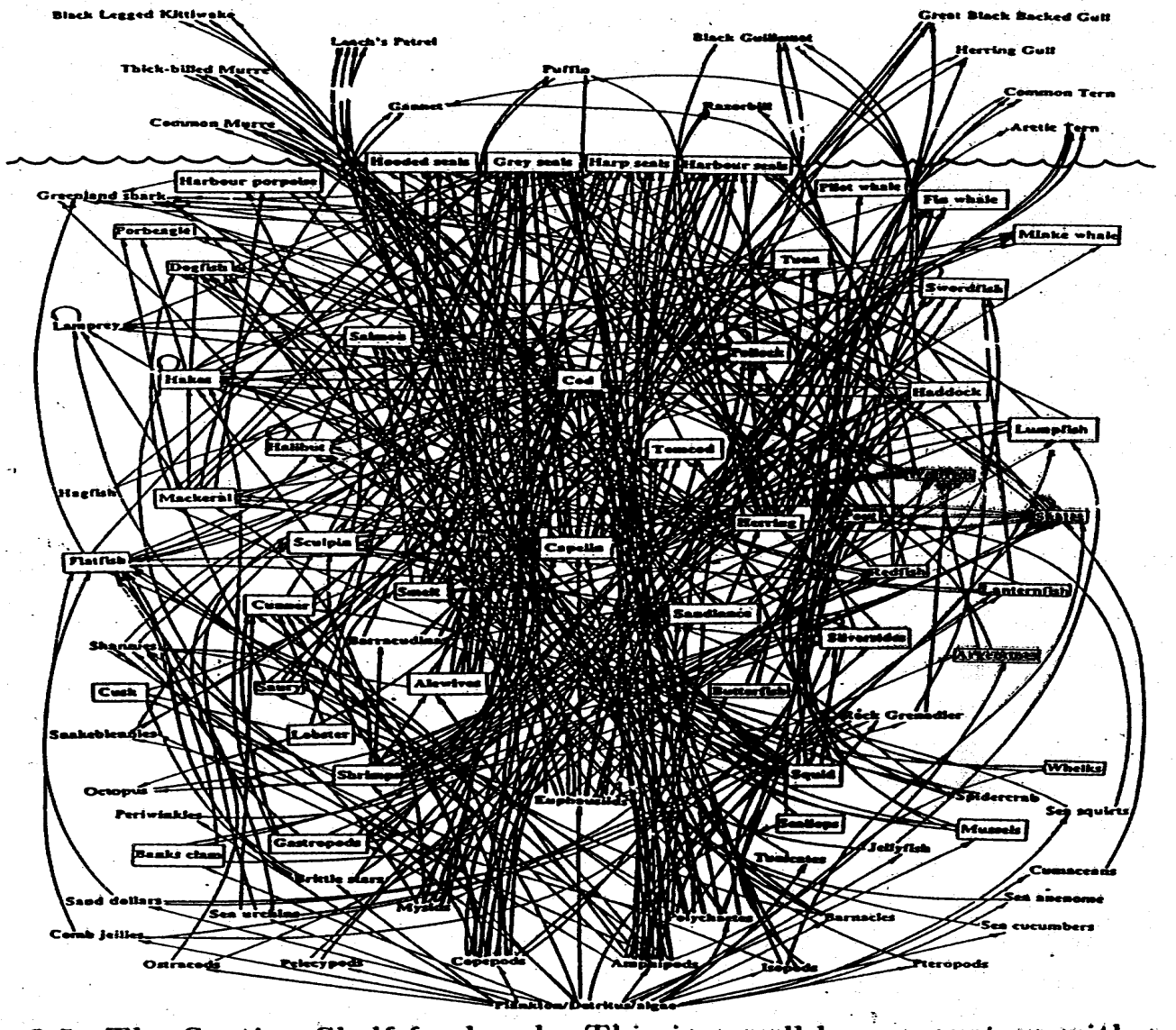


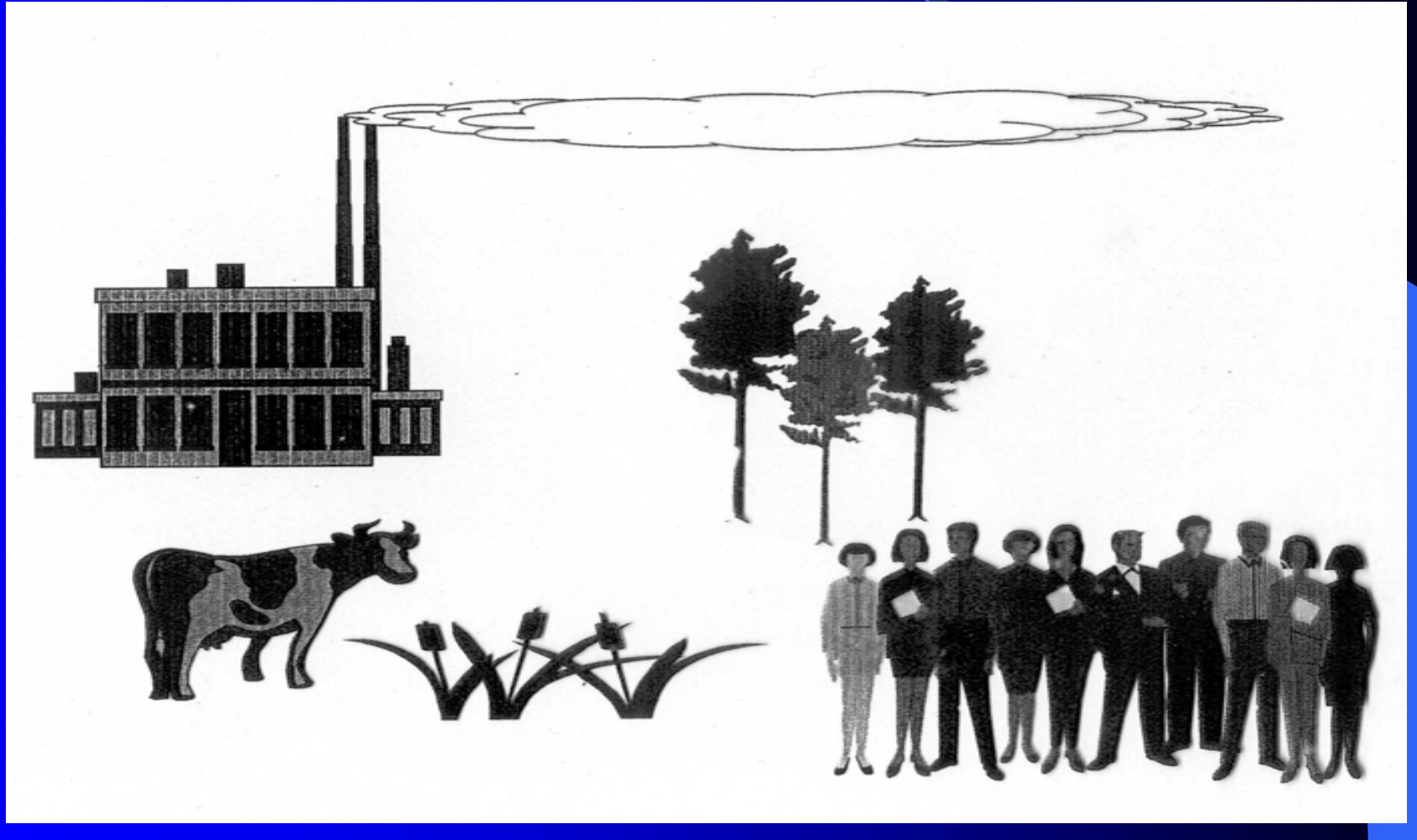
Figure 3.5: The Scotian Shelf food web. This is a well known system with a huge amount of links among species. It is quite obvious that in this ecosystem lacks any hierarchical principle and that a change in a single link may affect some species in an unexpected fashion.

Of Risk Assessment..

- A former director of the US EPA said:

- *"We should remember that risk assessment can be likened to the captured spy: if you torture it long enough, it will tell you anything you want to know"*

If you ask the wrong question – you get the wrong answer



An example of a ‘fact-free’ model in environmental chemistry

- ‘… summary data is presented of the estimates in the Environmental Statement for the worst case situation for the rate of deposition of various chemicals from the refuse to energy plant on local crops assuming continuous exposure. The human risk from consuming these is assessed for a hypothetical *maximally exposed individual*. This individual is presumed to consume largely (60% of total intake) vegetables grown in the area (eg: from allotments) of the maximum impact of the stack plume (i.e. having maximum long term GLC values). As discussed above, continual emission is presumed. These are worst case assumptions. (Professor J. W. Bridges)

Areas of potential GM hazard

- Genetic instability – transgenes are inherently unstable
- Horizontal gene transfer (eg antibiotic resistance)
- Pleiotropic effects: allergy, toxicity

Substantial Equivalence

- A chemical test of composition
- Not predictive of biological effects
- What is needed is knowledge of:
  - Allergenicity
  - Unpredicted toxicological effects

‘Risk Assessment’ from Ag-Bio manufacturers

ii. Potential for gene transfer

Brief Description of Hazard	Potential Harmful Effects	Probability of Realisation	Risk of damage
Transfer by Pollen to Plants	Low	Negligible	Effectively zero
Transfer by Vector to Plants	Low	Negligible	Effectively Zero

Pollen production will be prevented by the removal of whole "bolter" (flowering) plants before flower formation. The trials will be checked periodically for the presence of bolters.

There are no precedents to support the hypothesis that genetic material may be transferred by a virus/aphid vector interaction.

iii. Phenotypic and genetic stability

Brief Description of Hazard	Potential Harmful Effects	Probability of Realisation	Risk of Damage
Phenotypic Modifications	Negligible	Low	Effectively Zero

Previous experiments with these transformed lines of cultivated beet have shown the phenotypic stability of this material over several generations. Any phenotypic modifications in subsequent generations would not be expected to enhance the ecological success of the modified plants and would not be expected, therefore, to adversely affect the environment. In any event, bolter removal will ensure no propagation of unexpected modifications.

Monsanto risk assessment for GM sugar beet in Eire

D. EVALUATION OF OVERALL RISK

i. Risk of individual hazards causing damage

Description of Hazard	Risk of Damage
Theft of plant material from trial site	Low
Grazing of plant material by wildlife	Low
Movement of plant material on field machinery	Low
Loss of plant material during transit incident	Effectively Zero
Loss of viable plant material during sampling/processing	Effectively zero
Vegetative regeneration	Effectively Zero
Gene transfer by pollen to other relative plants	Low
Gene transfer by virus/aphid vectors to other plants	Effectively Zero
Phenotypic modification caused by gene insertion/tissue culture	Effectively Zero
Transfer of harmful characteristics from donor organisms	Effectively Zero
Use of *Agrobacterium tumefaciens* vector	Effectively Zero
Ingestion of glyphosate tolerance proteins	Effectively Zero
Ingestion of beta glucuronidase protein	Effectively Zero
Selective advantage of modified beet	Low

ii. Summary assessment of all risks

The overall risk of damage is assessed as low to effectively zero.

Chardon LL – T25 fodder maize

- Purified PAT protein taken from another plant species – Canola
- Fed to a non-relevant species – rat
- Irrelevant anti-nutrient, phytate, assessed
- Non-substantial equivalence ignored (changes in fatty acid expression)
- No whole food feeding trial to cattle

How long are the reassurances offered in a risk assessment good for?

- A low probability
- Given enough time
- Becomes a racing certainty

Standard format for risk assessments?

- Pro-forma listings of:
  - All hazards identified
  - Those hazards identified but not assessed
  - Those hazards not assessed but modelled
  - Areas of uncertainty identified
  - Levels of confidence in the results
  - Time scale over which the risk assessment can be considered to be valid

How much hazard assessment is being performed on GM crops?

- Dr Arpad Pusztai won a grant of £1.6 million from the Scottish Office to *develop* hazard assessment methods
- He has published his results in *Lancet*
- Industry did not like his results
- This type of work appears to have stopped!

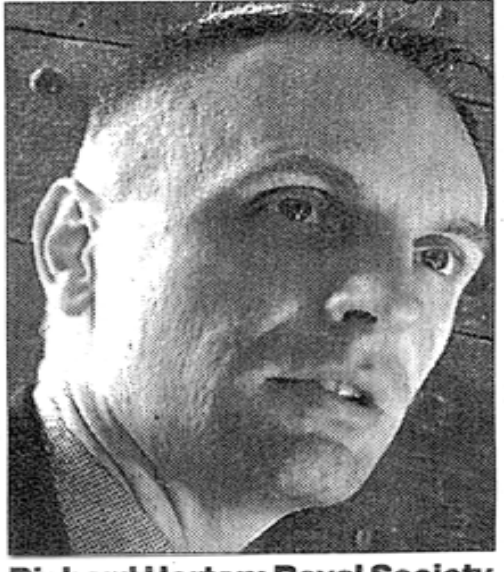
Peer pressure???

Top pro-GM food scientist threatened me, says editor

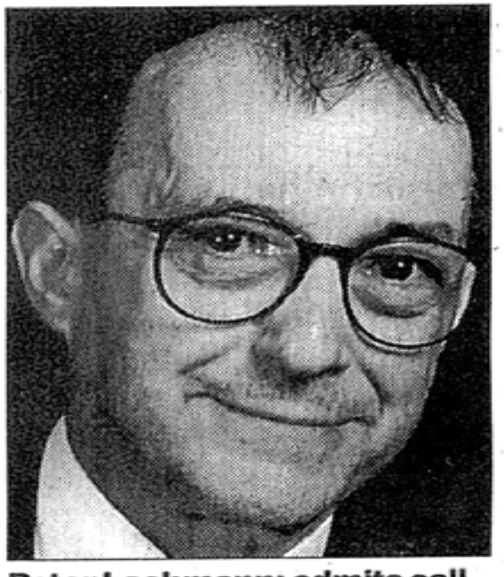
Guardian 1/11/99

◂ **Page 1** publishing both papers. He said there was intense pressure on the Lancet from all quarters, including the Royal Society, to suppress publication. The campaign, he said, was "worthy of Peter Mandelson".

The Guardian has learned that these interventions are taking place in an unusual context. According to a source the Royal Society science policy division is being run as what appears to be a rebuttal unit. The senior manager of the division is Rebecca Bowden, who coordinated the highly critical peer review of



Richard Horton: Royal Society behaving 'like a star chamber'



Peter Lachmann: admits call to editor but denies th. eats

Coin-operated consultants?

- "All policy makers must be vigilant to the possibility of research data being manipulated by corporate bodies and of scientific colleagues being seduced by the material charms of industry. Trust is no defence against an aggressively deceptive corporate sector."
- - THE LANCET, April 2000

GOVERNMENT WATCHDOG GIVES STARK WARNING OVER GM WEEDS

- Tues 5 February 2001

- Super weeds, resistant to a number of herbicides, are already resulting from growing genetically modified crops, a new report from the UK Government's nature watchdog warns today. The findings will increase fears about the threat posed by GM crop trials growing in the UK to neighbouring crops and the environment.

GOVERNMENT ADMITS GM CROP SEPARATION DISTANCES ARE INADEQUATE
18th January 2002

- In a little-publicised response [published 17/1/02] to a critical report into the controversial GM farm scale evaluations (FSE),Environment Minister, Margaret Beckett says that:the results of the GM evaluations are insufficient to allow for the commercial growing of GM crops, there will be a public debate on whether GM crops should be commercially grown; there is a case for separation distances to be massively increased to protect neighbouring farmers. The admissions are contained in the Government's response to the Agriculture and Environment Biotechnology Commission's report:
- Crops on trial (www.aebc.gov.uk).

Separation Distances

- The current separation distances between GM and non-GM crops have been set to ensure contamination is a maximum of 1% (50 metres for conventional oilseed rape). The Government now agrees " there is a case for separation distances to be greater so as to ensure a maximum of, for example, 0.1% cross-pollination ". This would represent a huge increase in separation distances. The EC proposed last year that for oilseed rape seed production to achieve a contamination threshold of 0.3% would require a separation distance of 5km.

Political pressure ??

Ministers to promote genetic engineering

A LEAKED Government document shows that ministers are intent on promoting the "benefits" of genetically-modified food and genetic engineering to the public.

by DAVID CRACKNELL

Political Correspondent

their deliberations about whether to sanction new scientific processes.

parent" and a mechanism found for identifying conflicts of interest.

Ministers have also decided to strengthen the role of the Government's

No risk is acceptable if it is avoidable

- Biotech industry spokesmen tell us that "nothing is 100% safe"
- Traditional foods have been tested for thousands of years, GM foods for < 10 years
- We are being asked to risk eating GM food (not 100% safe) for no immediate benefit except to the manufacturers
- The rationale is that "we are all going to starve"

Precaution – the best option

- Decision on the balance of probabilities
- Reverse onus
- Strict liability for “Pervasive Technologies”
- Prior debate on a societal level before the development of new pervasive technologies
- The use of risk assessment only in situations where it is appropriate