IRGC/OECD/UCL Conference on Planned Adaptive Regulation
Panel 1.2 Planned Adaptation
8 January 2016
Lessons of the Past: Exemplary Cases and Cautionary Tales

Professor Kenneth A. Oye
Program on Emerging Technologies
Massachusetts Institute of Technology

Exemplary Cases	Cautionary Tales
Netherlands Dikes	
Japan Seismic Codes	
EMA Adaptive Pathways	
Aviation Safety (NTSB)	NRC NASA Shuttle
EU Prion Disease (BSE)	US Agriculture BSE
EPA PM2.5	NIH-FDA Transfats

This presentation is based on research and workshops supported by NSF, EPA, MIT Center for Biomedical Innovation and IRGC; and on feedback on presentations and panels with WHO, UNBWC, NRC Life Sciences Board, NSABB, EMA and OECD.

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ELEMENTARY PRINCIPLES FOR GOVERNING EMERGING RISKS

PROSPECTIVELY PLANNED ADAPTATION

- Both phenomena being regulated and effects of regulatory policies are not well understood upfront. Understandings change with observations on use.
- Policies should be proactive and adaptive, engaging with priors on risks/benefits and updating as understandings of risks and benefits evolve.

OBSERVING/SENSING/REVEALING

- Parties differ in their interest in harvesting and sharing information needed to evaluate benefits/risks.
- Policies should create incentives and cut disincentives to reveal information needed for risk management (research funding, liability and IP law).

CREDIBLE KNOWLEDGE ASSESSMENT

- Conflicts of interest, organizational inertia and prior beliefs typically bias observation and assessment.
- Policies should provide for credible and legitimate assessment of scientific and technical information under complexity, uncertainty and controversy.

DISTINCTION BETWEEN REACTION AND PLANNED ADAPTATION

Netherlands 1953

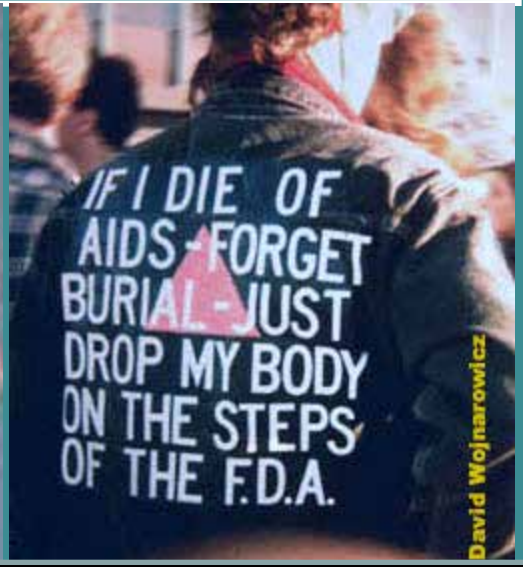
Government diagnosed and fixed flaws in dikes and flood gates and created ongoing adaptive review.

Kobe 1995

Government diagnosed specific flaws in seismic building codes and created ongoing adaptive review.

DRUG SAFETY AND ACCESS CRISES PROMPT PIECEMEAL CHANGE

CRISES	RESPONSES
Thalidomide	Approval based on efficacy/safety evidence from trials Strengthen adverse effects reporting (AERS/VARS)
Accutane™ and Vioxx™	Controls to limit known risks (REMS/RMS) Increased attention to safety and risk management Strengthen active & passive surveillance (Sentinel)
HIV, Cancer	Accelerated Approval/Conditional Marketing Authorization Use of un-validated biomarkers



nature publishing group

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See COMMENTARY page 378

Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval

H-G Eichler[1,2], K Oye[2,3,4], LG Baird[2], E Abadie[5], J Brown[6], CL Drum[2], J Ferguson[7], S Garner[8,9], P Honig[10], M Hukkelhoven[11], JCW Lim[12], R Lim[13], MM Lumpkin[14], G Neil[15], B O'Rourke[16], E Pezalla[17], D Shoda[18], V Seyfert-Margolis[14], EV Sigal[19], J Sobotka[20], D Tan[12], TF Unger[18] and G Hirsch[2]

Traditional drug licensing approaches are based on binary decisions. At the moment of licensing, an experimental therapy is presumptively transformed into a fully vetted, safe, efficacious therapy. By contrast, adaptive licensing (AL) approaches are based on stepwise learning under conditions of acknowledged uncertainty, with iterative phases of data gathering and regulatory evaluation. This approach allows approval to align more closely with patient needs for timely access to new technologies and for data to inform medical decisions. The concept of AL embraces a range of perspectives. Some see AL as an evolutionary step, extending elements that are now in place. Others envision a transformative framework that may require legislative action before implementation. This article summarizes recent AL proposals; discusses how proposals might be translated into practice, with illustrations in different therapeutic areas; and identifies unresolved issues to inform decisions on the design and implementation of AL.

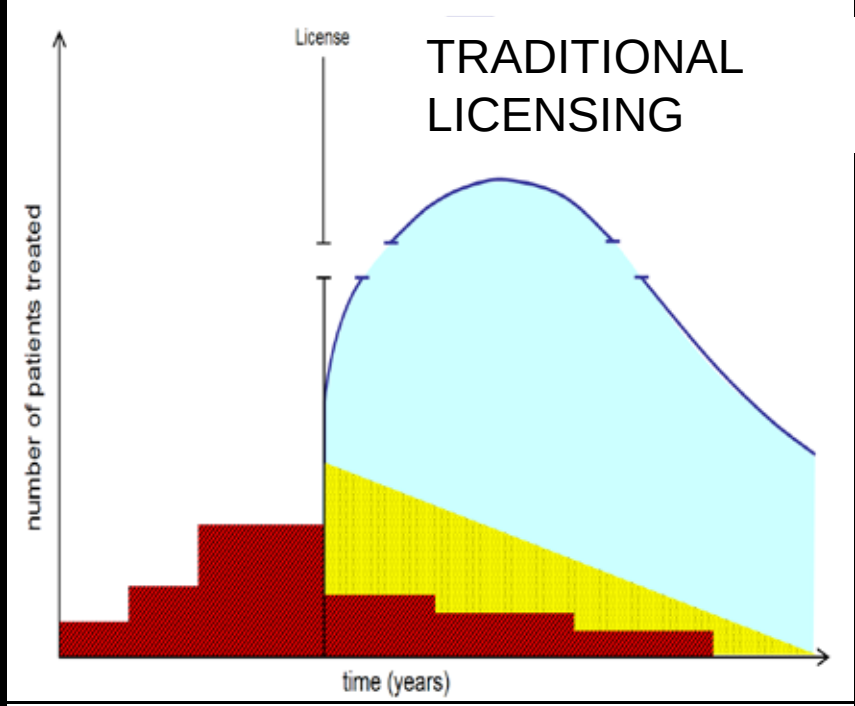
ADAPTIVE LICENSING
Patient experience contributes to evidence development

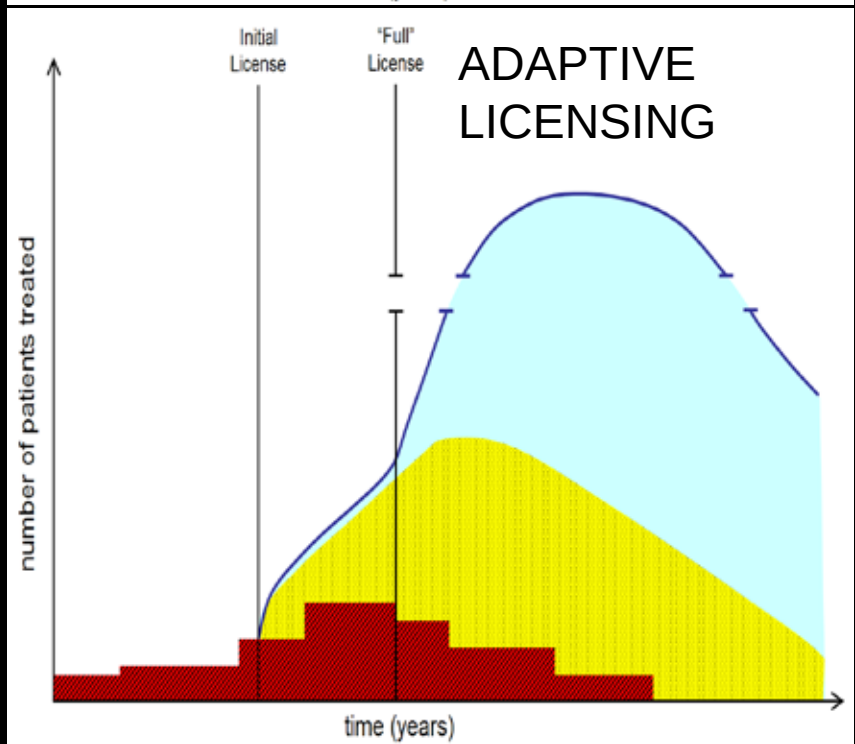
<u>FRONT END – PRE MARKET</u>
Earlier approval
Conditional
Limit to patients on benefit/risk

<u>BACK END – ON MARKET</u>
Strengthen observation
- Registries
- EHRs

Analyze safety and effectiveness
Adapt label and license

KEY
Patients in interventional studies
Patients treated but unobserved
Patients treated and observed





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COMMERCIAL AVIATION

1975 US LEGISLATIVE REFORM

"No Federal agency can properly perform such functions unless it is totally separate."

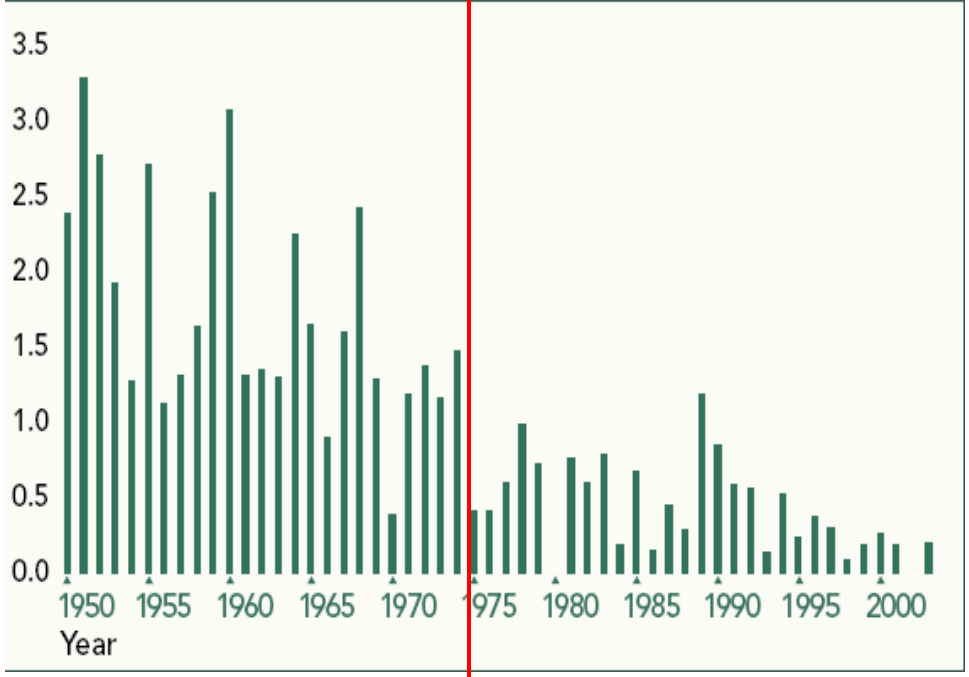
FAA certifies, NTSB investigates

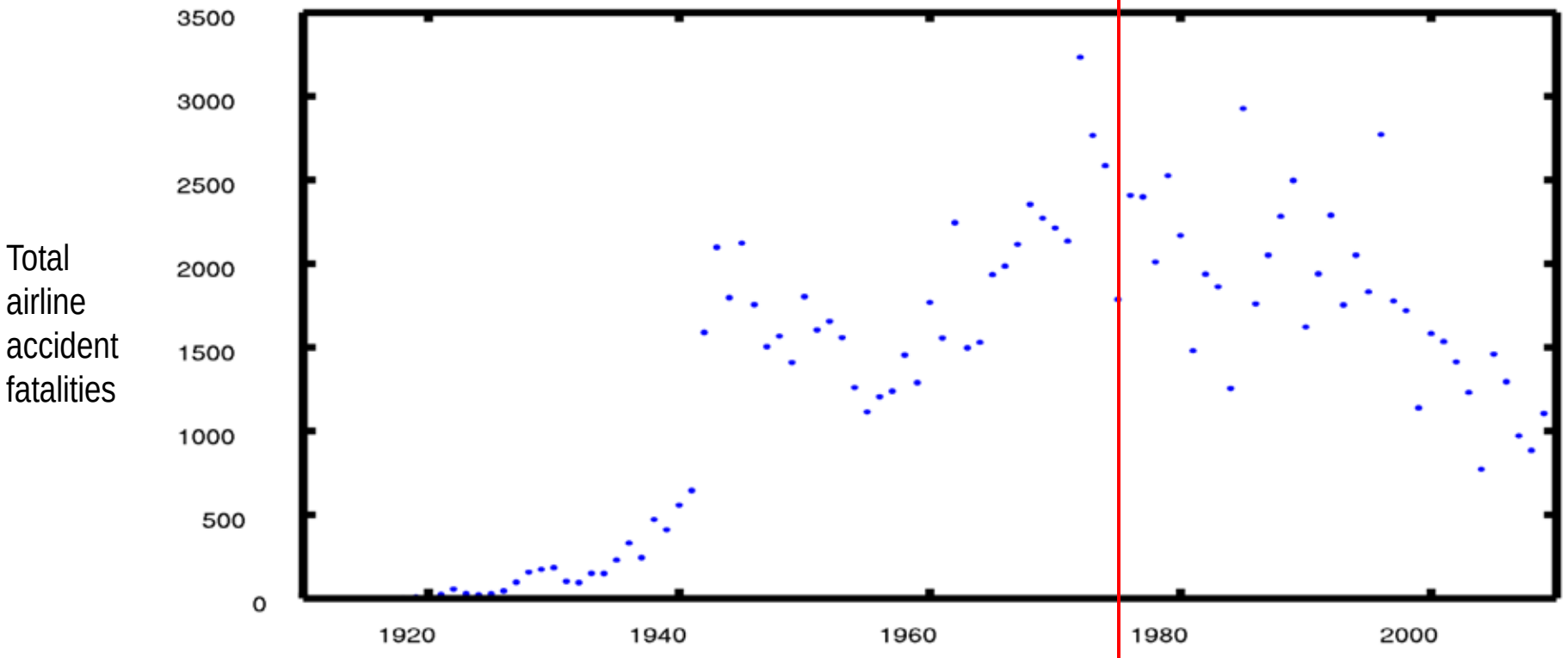
Examine accidents + near misses

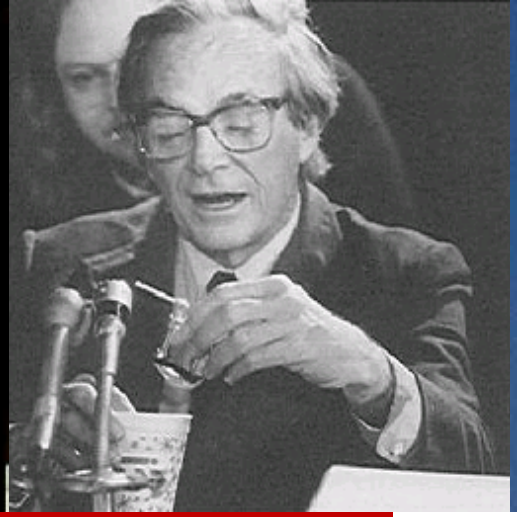
NTSB recommends

FAA/makers/airlines usually act

- Why was reform demanded?
- Did the reform work?







SHUTTLE – FIXED O-RING, DID NOT FIX NASA

Old Story - Richard Feynman on O ring failure

New Story - NAS on NASA design process

1986 Challenger disaster

1986 Rogers Commission / Feynman

1988 NAS advised NASA to adopt dynamic testing and experimentation process to inform adaptive risk management system

1989 NASA ignored NAS, chose static tests of safety without adaptive elements

2003 Columbia disaster

- Why did NASA reject NAS proposal?
- Was adaptive experimental approach needed?

Collected Reports of the Panel on Technical Evaluation of NASA's Redesign of the Space Shuttle Solid Rocket Booster

of the

Committee on NASA Scientific and Technological Program Reviews

Commission on Engineering and Technical Systems

National Academy Press
Washington, D.C. 1988

EU TSE ROADMAP – STRUCTURED SENSING AND POLICY FEEDBACK

We have come to the stage that amendments of certain measures could be envisaged without endangering the health of the consumer or the policy of eradicating BSE, provided that the positive trend continues and scientific conditions are in place. Indeed different indicators already suggest a favourable trend in the BSE epidemic and a clear improvement of the situation in recent years due to the risk reducing measures in place. Furthermore, inspection reports indicate that implementation of BSE requirements in the Member States has improved. The main indicators are presented in Charts 1 -3 of Annex I.

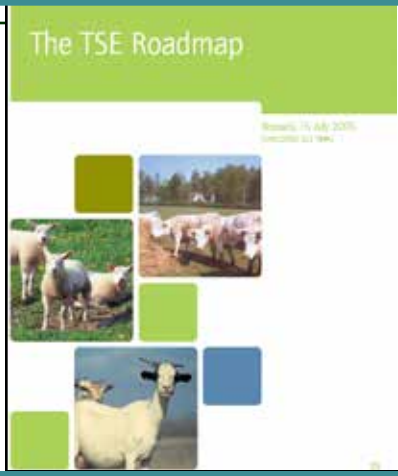
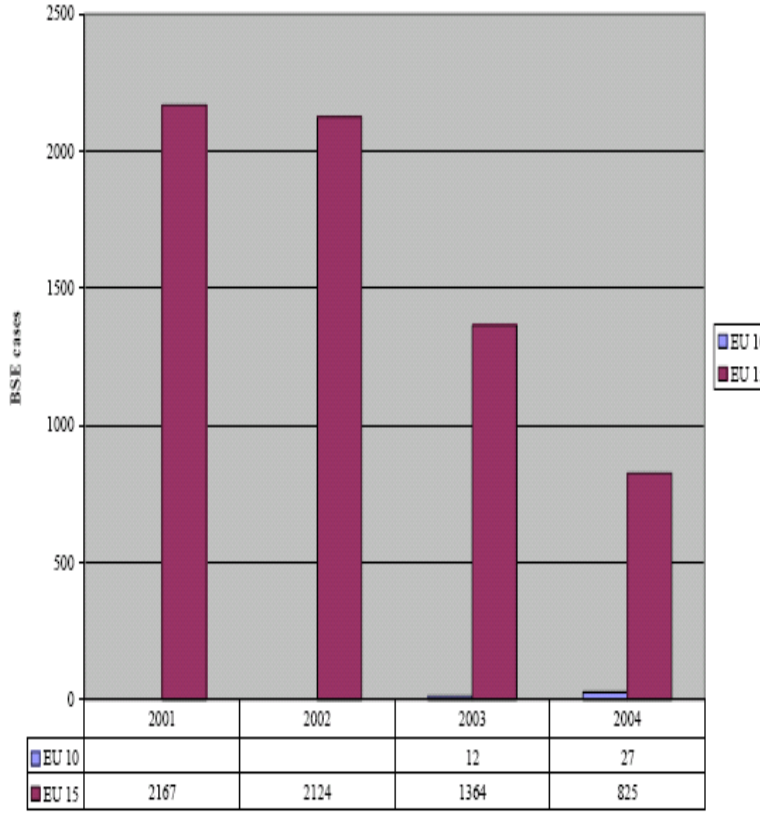
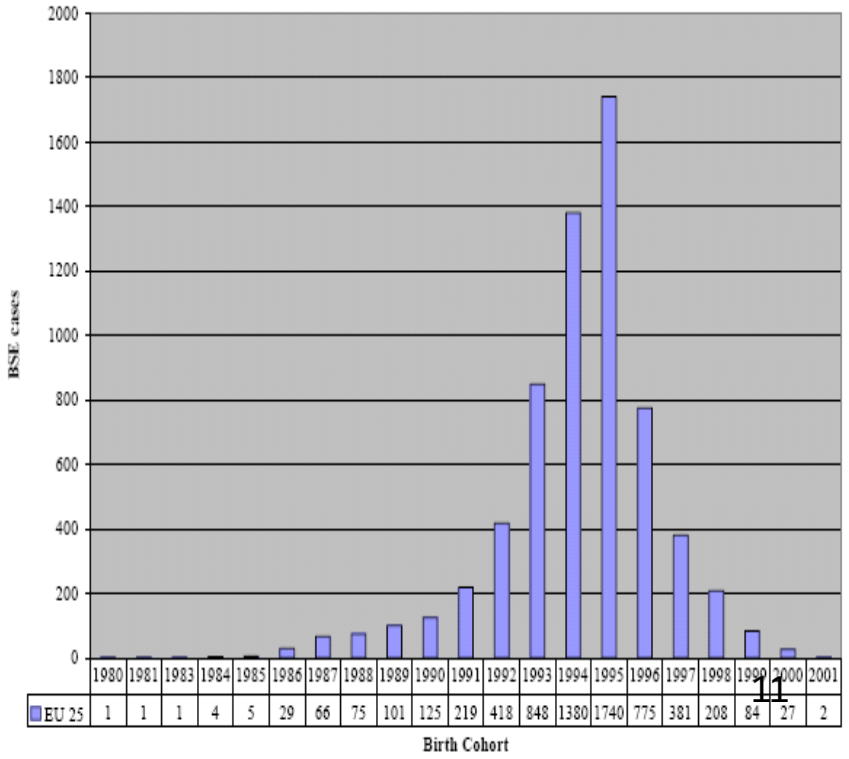


CHART 1: EU BSE CASES 2001 TO 2004



	2001	2002	2003	2004
EU 10			12	27
EU 15	2167	2124	1364	825

CHART 2: EU BSE CASES BY BIRTH COHORTS



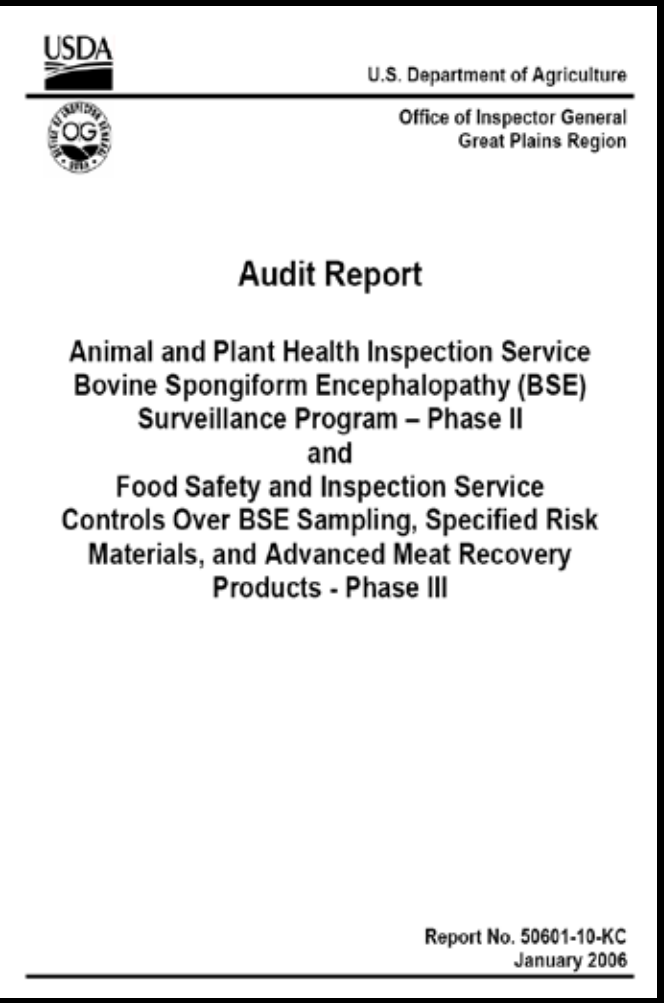
	1980	1981	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001
EU 25	1	1	1	4	5	29	66	75	101	125	219	418	848	1380	1740	775	381	208	84	27	2

US BSE SURVEILLANCE AND TESTING – WEAK SENSING

BSE TESTING	US	JAPAN
PERCENT TESTED	.05 percent	100.00 percent
TYPE TESTED	sample of downers	all cattle prefectures < 20 mo national > 20 mo
SCREENING TEST	BioRad rapid reaction	BioRad rapid reaction
OLD CONFIRM TEST	IHc	IHC + Western Blot
NEW CONFIRM TEST	IHC + Western Blot	IHC + Western Blot
BSE CASES	2 cases	20 cases

*IHC = ImmunoHistoChemistry

US BSE SURVEILLANCE AND TESTING – WEAK SENSING



USDA

U.S. Department of Agriculture

Office of Inspector General
Great Plains Region

Audit Report

Animal and Plant Health Inspection Service
Bovine Spongiform Encephalopathy (BSE)
Surveillance Program – Phase II
and
Food Safety and Inspection Service
Controls Over BSE Sampling, Specified Risk
Materials, and Advanced Meat Recovery
Products - Phase III

Report No. 50601-10-KC
January 2006

[APHIS officials] justified their decision to not do additional testing because the IHC test is internationally recognized as the gold standard of testing. Also, they believed that conducting additional tests would undermine confidence in USDA testing protocols. p iii-iv

The additional tests recommended by NVSL scientists, but not approved by APHIS Headquarters officials, were the IHC using other antibodies (IHC testing using different antibodies ultimately produced positive results); IHC testing of additional regions of the brain (the cerebellum tested positive); regular and enriched (OIE-like) Western blots (the obex and cerebellum tested positive); and variable rapid tests (the obex and cerebellum tested positive with two different rapid tests). p 33.

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EPA NATIONAL AMBIENT AIR QUALITY STANDARDS

- Review process to reassess standards based on best available evidence
- Research funding to reduce uncertainty and improve best available evidence

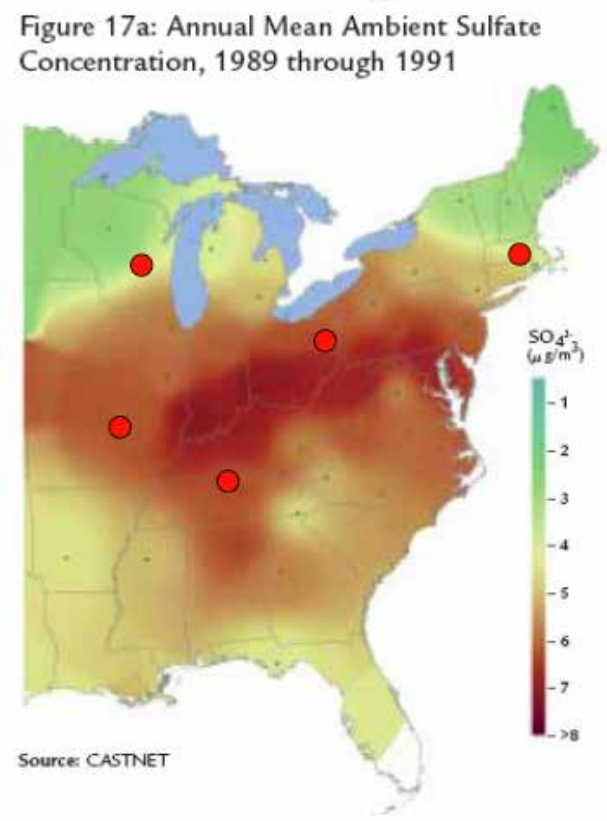
HARVARD SIX CITIES

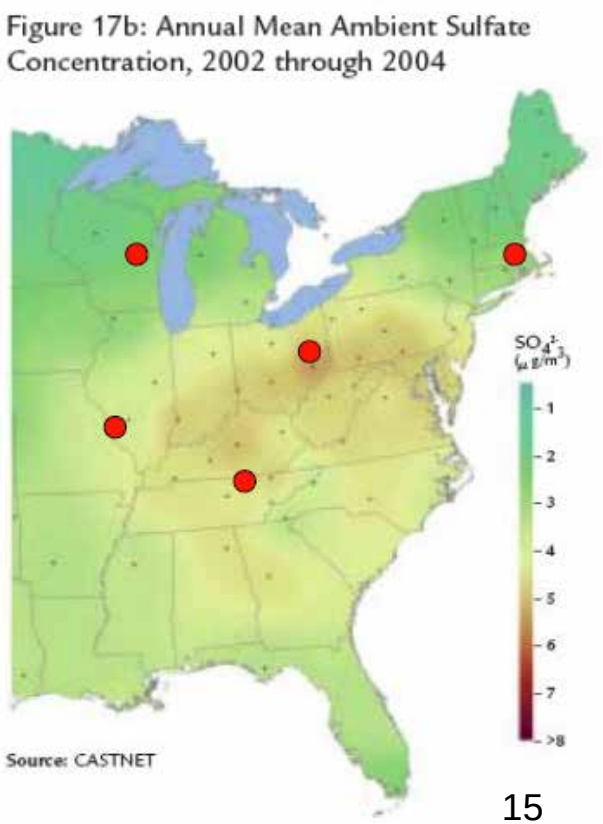
8000+ subjects in panels

Adjusted mortality risk ratios

- Age, Sex
- Cigarette Smoking
- Occupational Exposure
- Education
- Body Mass Index
- Chronic Disease

STUDIES IN 80S AND 90S CAPTURE POLICY EFFECTS





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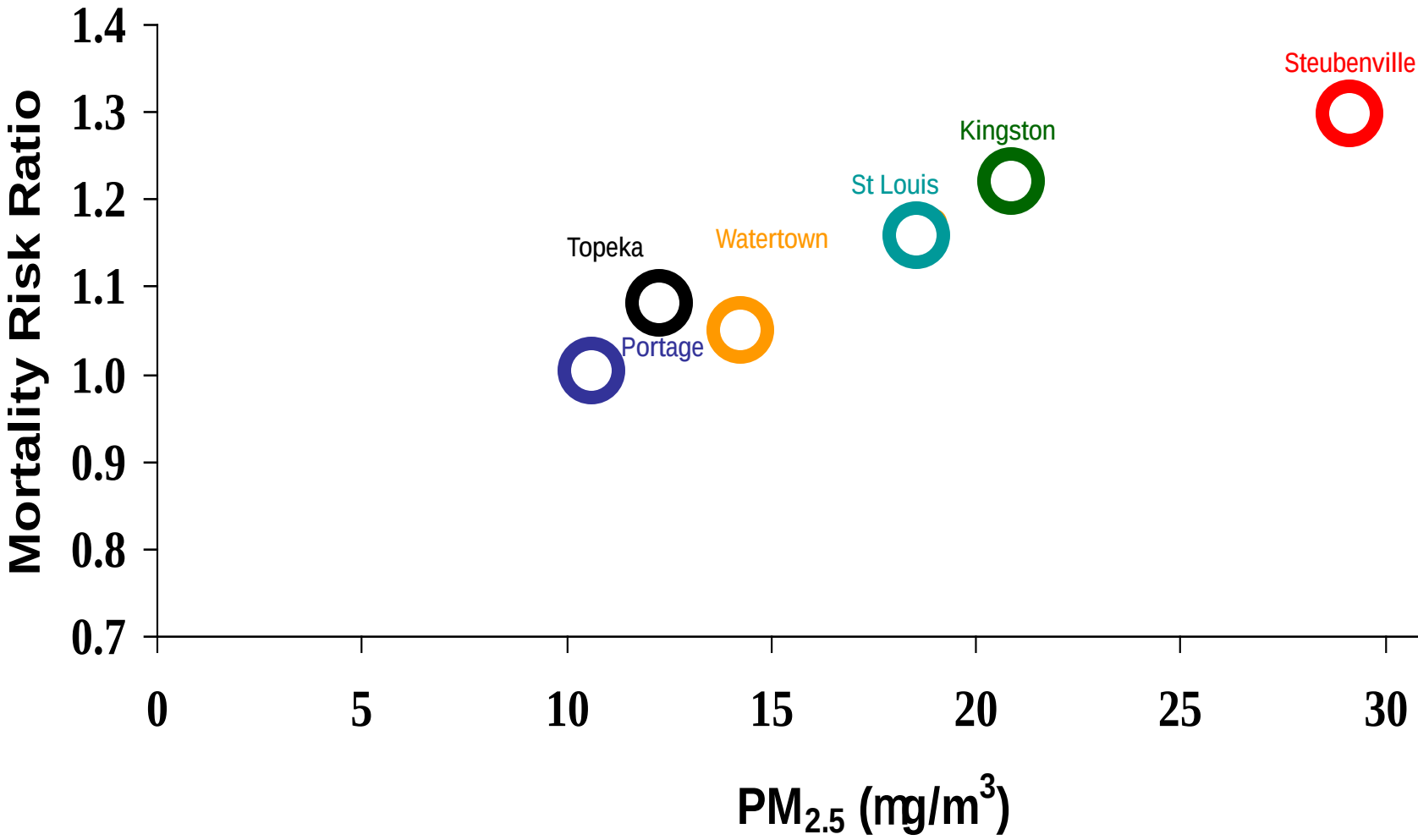
Six Cities Cohort Follow-up Study
1990 - 1998



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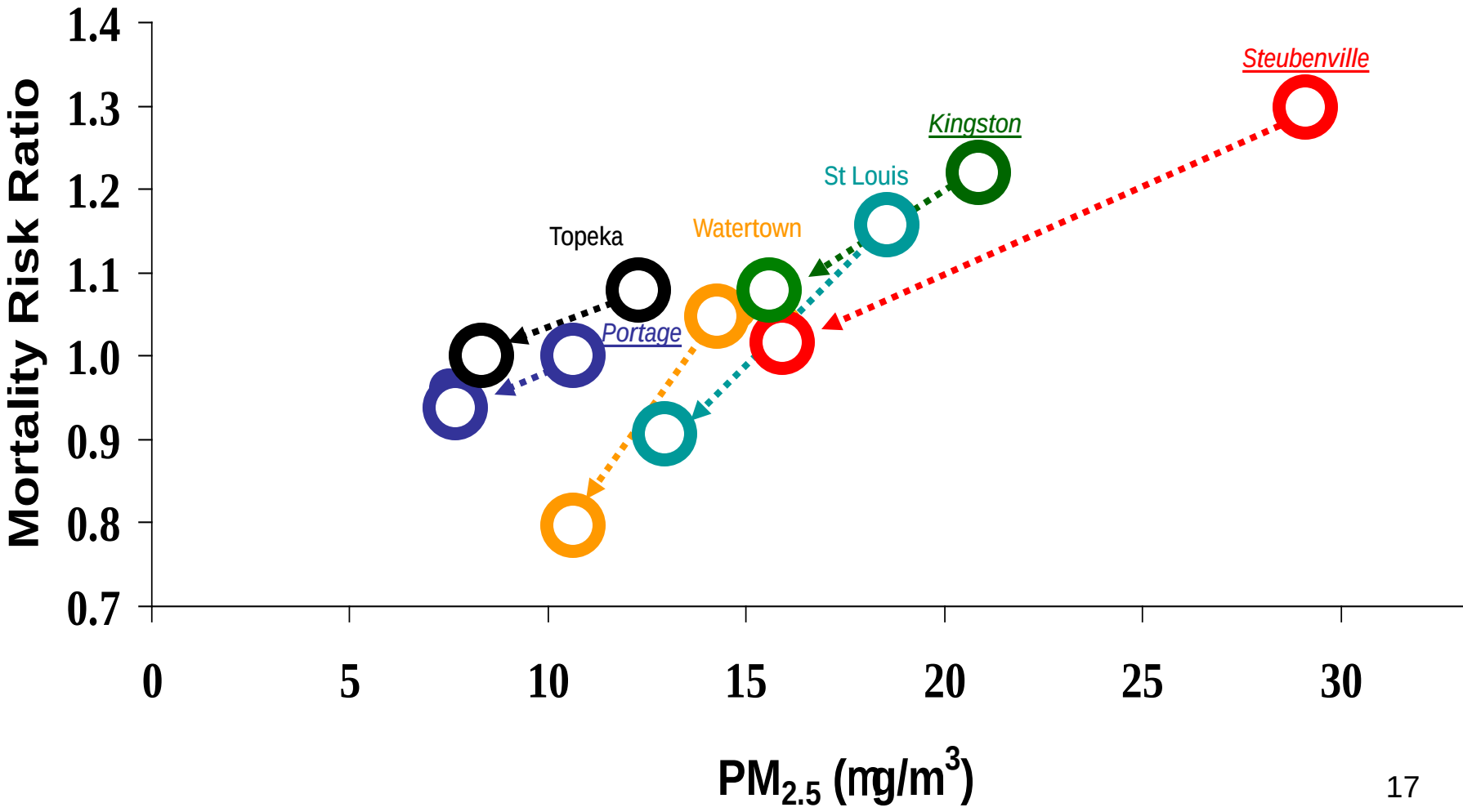

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HEI

SPECIAL REPORT

HEALTH EFFECTS INSTITUTE

July 2000

Includes Errata Sheet Of 11-01-01

Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality

A Special Report of the Institute's Particle Epidemiology Reanalysis Project

Executive Summaries and Commentary

OWNERS OF BANKED ALLOWANCES BENEFIT FROM QUOTA CUTS

Figure 3: SO_2 Emissions and the Allowance Bank, 1995–2004

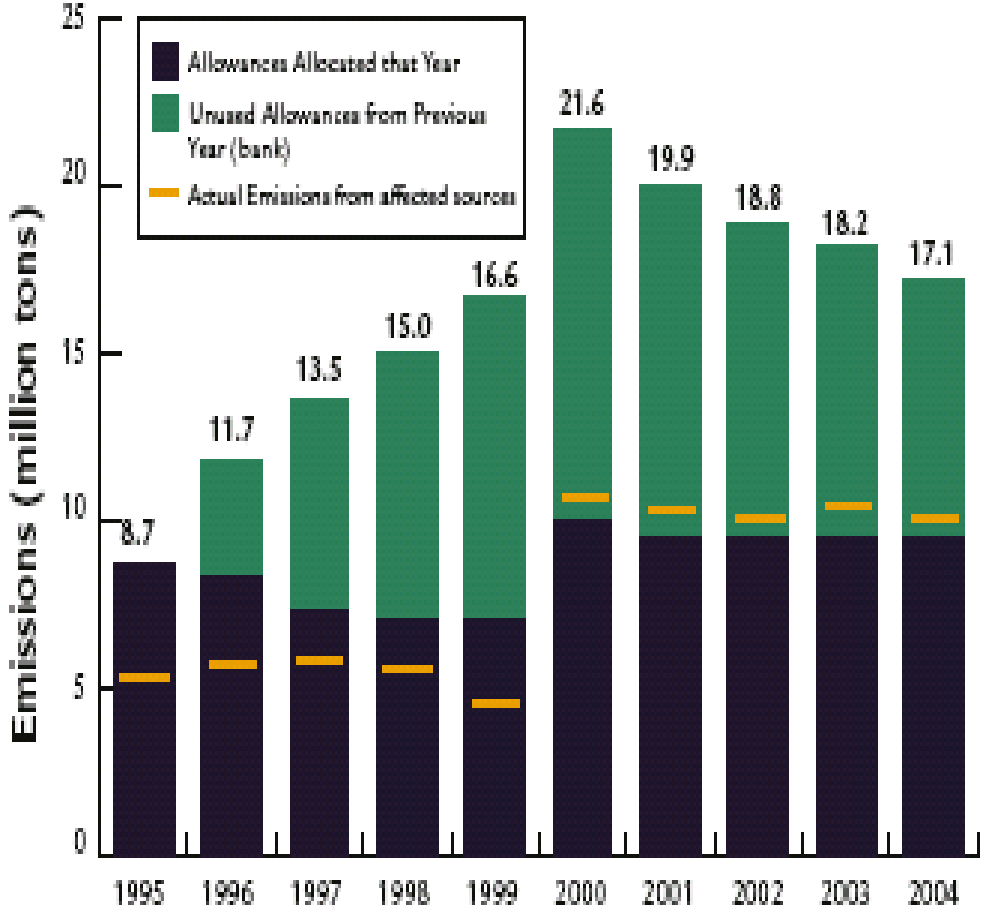
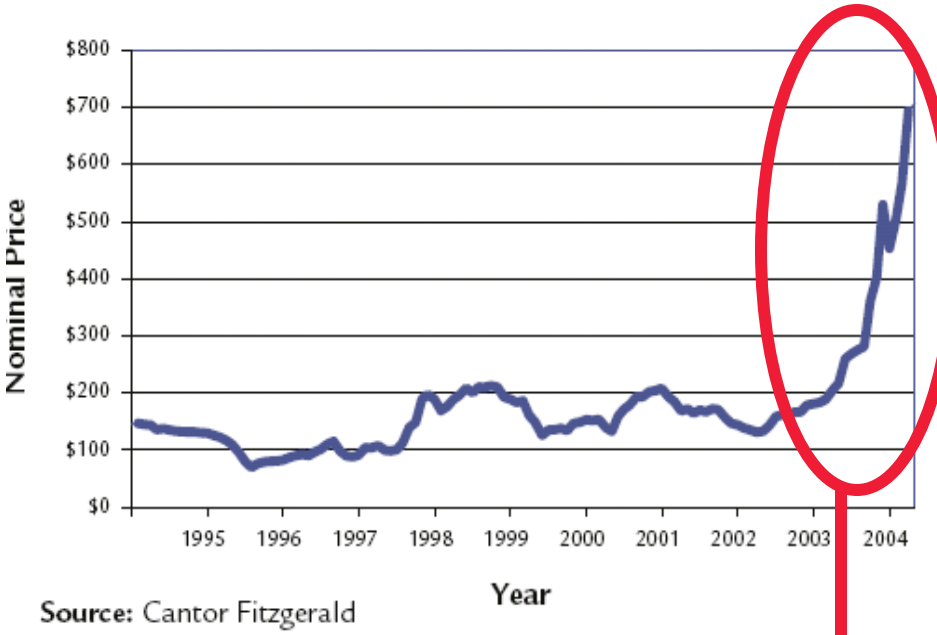


Figure 6: SO_2 Allowance Prices



Source: Cantor Fitzgerald

The price of an allowance increased sharply during 2004, ending the year at about $700 after beginning the year at about $215 (see Figure 6). The increase primarily occurred because of EPA's Clean Air Interstate Rule (CAIR). CAIR requires further SO_2 reductions from sources in many eastern U.S. states beginning in 2010, and the market has already begun to factor the marginal cost of future compliance with CAIR and the future value of banked allowances today.

Figure 3 & 6, US EPA, Acid Rain Program 2004 Progress Report.

TRANSFATS AND CORONARY HEART DISEASE: A CAUTIONARY TALE

1972-77 AMA replace animal fats with transfats; FDA declare transfats safe

2003-13 FDA label transfats; declares transfats not safe; bans transfats

Cost of lag: 7000 to 30000 extra deaths per year from coronary heart disease

KRAFT®

PARKAY
The Flavor Says "Butter!"

Becel

Unilever

1957 T-FAT HUMAN TISSUE JOHNSTON, JOHNSON, KUMMEROW SCIENCE

Occurrence of trans Fatty Acids in Human Tissue

Except for small amounts of *trans* fatty acids in animal fats, dietary fats are composed of unsaturated fatty acids of *cis* geometric configuration. In 1928, Ber-

"In view of the current controversy on the relationship of 'hard' vs 'soft' fats, it would seem necessary to determine what effects, if any, *trans* fatty acids have on the normal metabolic process."

hydrogenation of vegetable oils (4); the shortenings and margarines which include these hydrogenated oils have been reported to contain as much as 23 to 42 percent of *trans* fatty acids (5). Furthermore, the isomers formed during selective hydrogenation are composed of a complex mixture of both geometric and positional isomers (6). The consumption

a Soxhlet apparatus for 24 acetone and petroleum ether F) as solvents, the extracts over anhydrous sodium sulered, and the solvent was re- vacuum. The amounts of s in the lipid extracts were by the Jackson and Callen

trans fatty acids seem to ed (10). Furthermore, it een reported that *trans* cro- the preferred substrate for ed acyl CoA hydrase from 1). Presumably, therefore, ns fatty acids may be meadily as the *cis* fatty acids. view of the current contro- relationship of "hard" vs. 2), it would seem necessary

very on the relationship of "hard" vs. "soft" fats (12), it would seem necessary to determine what effect, if any, *trans* fatty acids have on the normal metabolic process.

PATRICIA V. JOHNSTON
OGDEN C. JOHNSON
FRED A. KUMMEROW
Department of Food Technology

and to Cecil A. Krakower, University of Illinois College of Medicine, Chicago, for supplying the samples of human tissue used in this study.

8. F. L. Jackson and J. E. Callen, *J. Am. Oil Chemists' Soc.* 28, 61 (1951).
9. R. T. Holman, *Proc. Conf. on Research, Council on Research, Am. Meat Inst. Univ. Chicago, 3rd Conf. 1951*, p. 1.
10. A. D. Barbour, *J. Biol. Chem.* 101, 63 (1933).
11. S. J. Wakil, *Biochim. et Biophys. Acta* 19, 497 (1956); J. R. Stern, A. del Campillo, A. L. Lehninger, *J. Am. Chem. Soc.* 77, 1073 (1955).
12. H. M. Sinclair, *Lancet* 270, 381 (1956).

YMPOSIUM: Nutritional Perspectives and Atherosclerosis

LIPIDS IN ATHEROSCLEROSIS

F. A. KUMMEROW
The Burnsides Research Laboratory, University of Illinois, Urbana, IL 61801 and The Harlan E. Moore Heart Research Foundation, Champaign, IL 61820

Table 3—Summary data on ten groups of swine fed the basal diet plus various fat and cholesterol supplements

Diet	Total serum lipid mg%	Serum cholesterol mg%	RBC L/O	Intima cholesterol mg/g	Athero-sclerosis[b] %	Lesions[c]
Basal	273 ± 12	95 ± 5	0.9	8.6	6.0	3(10)
+20% Beef tallow	331 ± 13	124 ± 5	0.6	8.0	5.2	1(11)
+20% Rearranged fat	342 ± 19	125 ± 8	2.3	8.9	3.8	0(11)
+20% Corn oil	276 ± 21	104 ± 7	2.4	9.0	5.0	2(12)
+10% Used fat and sugar	362 ± 26	131 ± 11	0.8	9.6	8.6	3(12)
+20% trans fat	388 ± 20	138 ± 9	0.7	10.4	10.0	7(12)
+20% Butterfat	332 ± 15	120 ± 7	1.0	7.2	7.3	2(9)
+Whole egg powder	303 ± 14	112 ± 5	0.8	7.7	4.8	1(11)
+Egg yolk powder	286 ± 13	98 ± 5	1.0	7.2	4.2	0(12)
+Crystalline cholesterol	245 ± 19	93 ± 3	1.3	9.1	5.2	2(12)

[a] Basal—1,745 lb ground yellow corn, 200 lb soybean meal, 55 lb lysine supplement, vitamin-mineral premix, egg powder fed at cholesterol equivalent of 500 mg/day/200 lb animal weight.
[b] Atherosclerosis—% of total area of aorta
[c] Lesions—number raised plaques.

1976 FASEB EVALUATION T-FATS

1976 FDA GRAS CERTIFICATION

Margo -
Keep n Toss

PB-266 280

SCOGS-70

EVALUATION OF THE HEALTH ASPECTS OF HYDROGENATED SOYBEAN OIL AS A FOOD INGREDIENT

1976

Prepared for

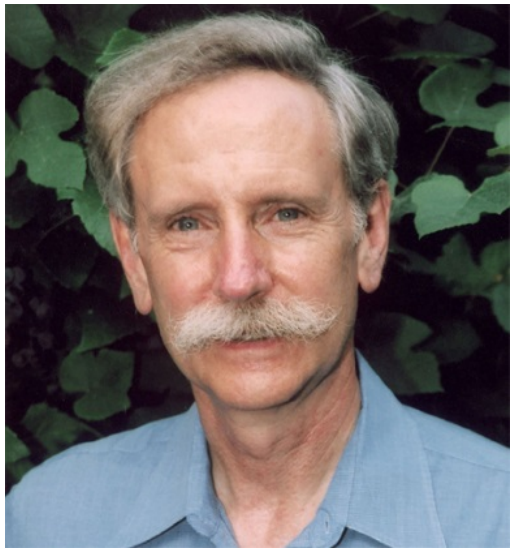
Bureau of Foods
Food and Drug Administration
Department of Health, Education, and Welfare
Washington, D. C.

FASEB
Federation of American Societies for Experimental Biology

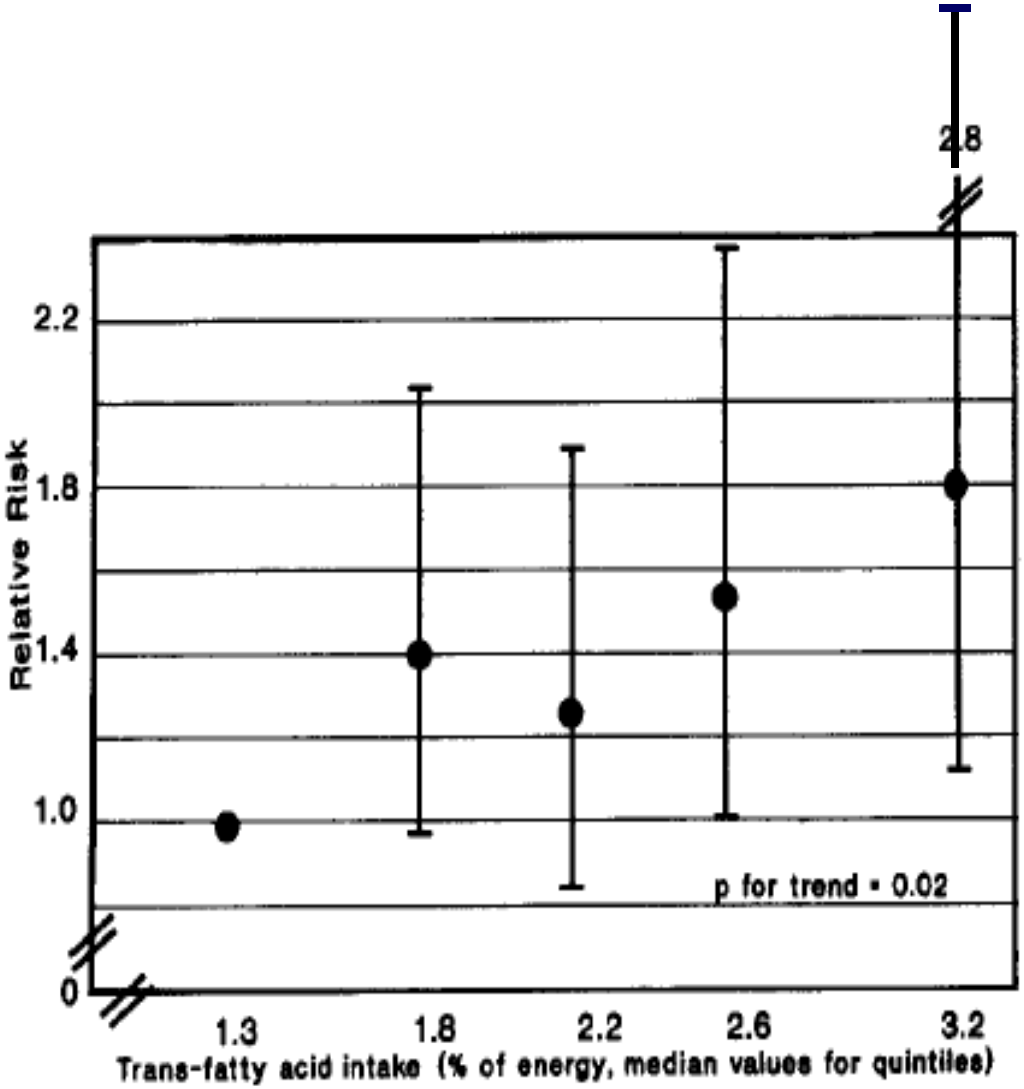
FDA

GENERALLY RECOGNIZED AS SAFE

There is no evidence in the available information on hydrogenated soybean oil that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when it is used as a direct or indirect food ingredient at levels that are now current or that might reasonably be expected in the future.



NATIONAL INSTITUTES OF HEALTH



Relative risk of CHD by *trans*-fatty-acid intake as percentage of total energy.

2001 JOHN GRAHAM OIRA PROMPT LETTER TO FDA

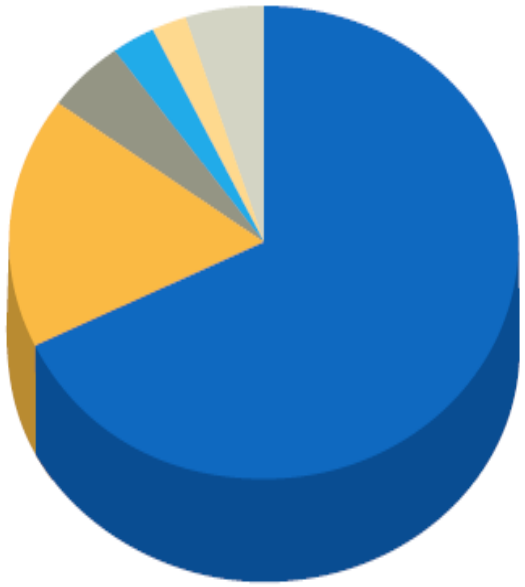
The key scientific premise was that trans fat consumption is linked to the development of coronary heart disease. To verify this premise, I asked my staff to consult the recent medical literature and reach out to three groups: the Department of Nutrition at the Harvard School of Public Health, the International Life Sciences Institute (a scientific group affiliated with the food industry), and the Center for Science in the Public Interest (a nonprofit advocacy group). All of these consultations reinforced our conviction that the FDA's scientific premise was sound.

ILSI International Life Sciences Institute

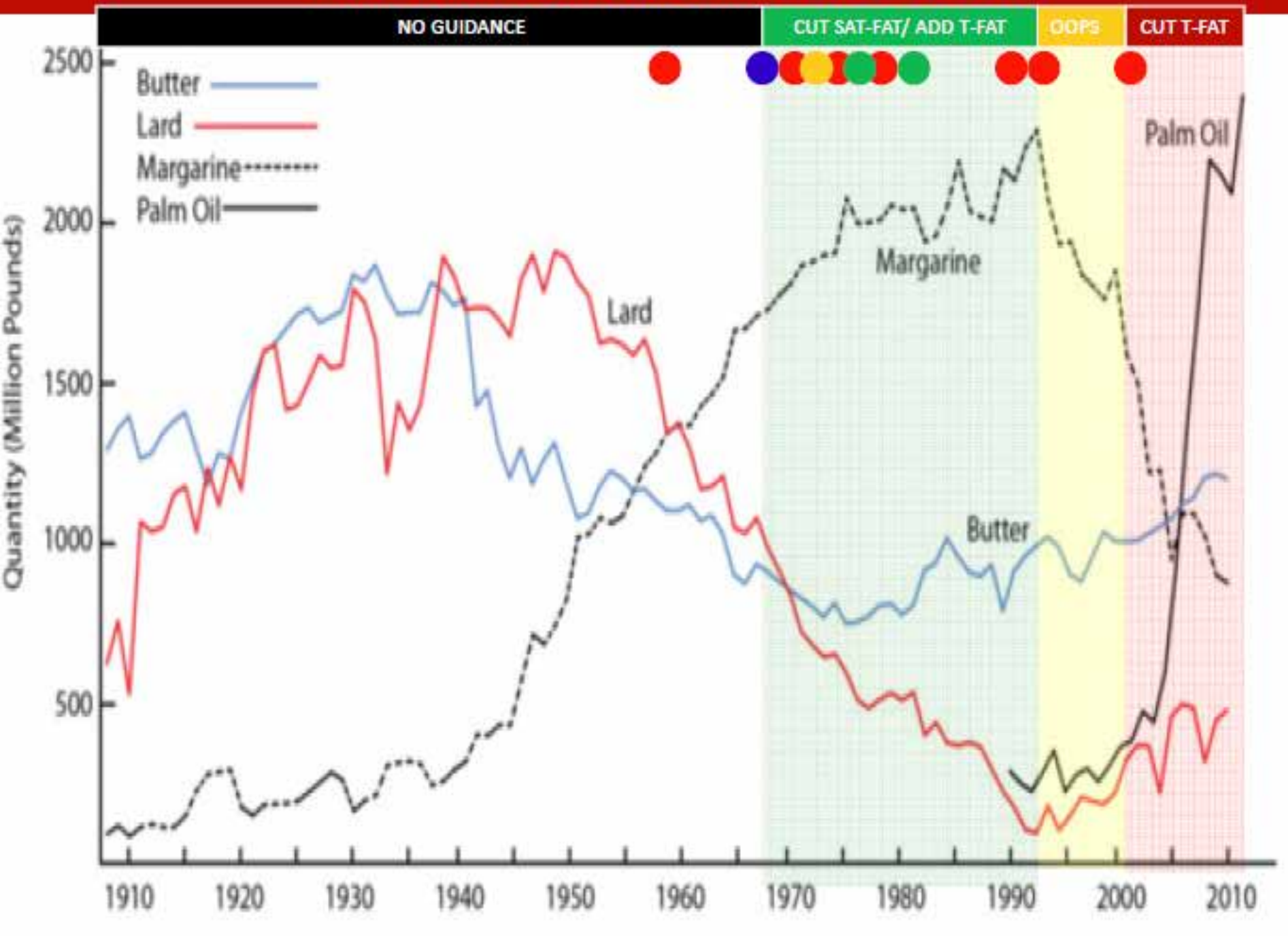
Harvard School of Public Health

Revenue Sources

- Member Support: 68%
- Grants & Contributions: 17%
- Publications: 5%
- Interest & Dividend Income: 3%
- Conference Registration: 2%
- Other Income: 5%



TRENDS IN US FAT CONSUMPTION 1909-2010



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SUBOPTIMAL ADAPTATION -- DEMAND AND SUPPLY CONDITIONS

INDUSTRIAL INTERESTS IN LIMITING ADAPTIVE POLICIES
- Existing regulations define an environment that has selected for existing firms
- Firms dislike policy variability and like predictability
- Firms fear regulatory variabllity will rachet up and not down

REGULATORY INTEREST IN LIMITING ADAPTIVE POLICIES
- Regulators usually prefer to stick with existing hard won regulations and SOPs
- Regulators do not wish to risk delegitimating rationales for existing policies
- Regulators fear variability will be seen as arbitrary increase demand for deregulation

LIMITED PUBLIC CAPACITY FOR ACCEPTING ADAPTIVE STRATEGIES
- Acknowledged uncertainty, shifting targets, changing rationales seen as vascilation
- Carter scorned for acknowledging complexity, Reagan loved for simplicity
- Need cleanly defined trigger event to spur reforms. . . .

CONCENTRATED INTERESTS IN SENSING, ASSESSING AND ADAPTING
- The National Academics, Think Tanks and some universities
- Some niche oriented firms

DIFFUSE INTERESTS IN MORE EFFICIENT AND EFFECTIVE REGULATION OF RISKS
- Public goods / free riding problem manifest
- Coalitions with odd couples necessary
- Communicative action and control of framing crucial

BACKUP

SOME RESULTS OF US FEDERAL CASE SURVEY (McCray et al 2010)

Of 32 candidate cases identified, the results of policies could be accounted for in 14, including 4 cases of planned adaptation and 10 cases of one-shot reviews .

Class One –"Changing Policies without Really Learning First" 3 cases

Three cases adjusted past regulatory decisions without systematic data on such basic matters as whether original estimates of benefits and costs are being realized in practice. For example, the DoT reported that it had shelved 70 regulations with no indication that such changes were preceded by substantive evidence-gathering on actual impacts.

Class Two – "Learning Without Really Reconsidering Policies" 7 cases

Seven cases entail attempts to understand effects of past regulatory decisions without using knowledge to improve policy. These include OMB reports on Costs and Benefits of Regulation, OMB request for nominations of federal rules needing change, EPA studies of health responses to ionizing radiation, and the Post Hoc Review Program of NHTSA.

Class Three –"Learning & Reconsidering Policies" 4 cases

Four cases meet full definition of regulatory feedback: NAAQS, radiation effects review, RDA review, and animal nutritional requirement review.

All four cases involve standard-setting, not rulemaking. Reviews determined whether a standard was still valid, without changing regulations governing private actions to achieve standards.

APPROACHES TO RISK GOVERNANCE UNDER UNCERTAINTY

Permissive

* Allow innovation unless environment, health, security are clearly compromised

After-the-fact reaction if crisis materializes; backlash may limit innovation

Examples: Post-Fukushima nuclear shutdown, US stasis on gene therapy

Precautionary

* Limit innovation unless environment, health and security are clearly protected

Diversion of innovation to less regulated areas may heighten risks

Examples: EU on GMOs, US on stem cell research, German genetic data protection

Planned Adaptive

* Prepare: Fund research to inform priors on benefits and risks
* Discriminate: Foster initial applications with most favorable priors
* Observe: Harvest and process information from initial experience
* Adapt: Learn from experience and update/correct practices

Exemplary Cases	Cautionary Tales
FAA-NTSB air safety	NASA shuttle
EU TSE policy	USDA BSE policy
EPA PM2.5	NIH FDA Transfats

PERMISSIVE: AFTER-THE-FACT REACTION TO HARMS

DDT “Silent Spring”	EPA banned chlorinated pesticides & herbicide
Challenger + Columbia	NASA fixed booster, did not engage in dynamic testing
Gene therapy	FDA restricted gene therapy after permissive testing
Trans fats heart disease	1957-1991 research, 2006-2013 FDA label and ban
Fukushima	Disaster, Japan shut nuclear plants

For Immediate Release: August 8th, 2007

Public Interest Group Calls for Public Disclosures in Gene Therapy Death

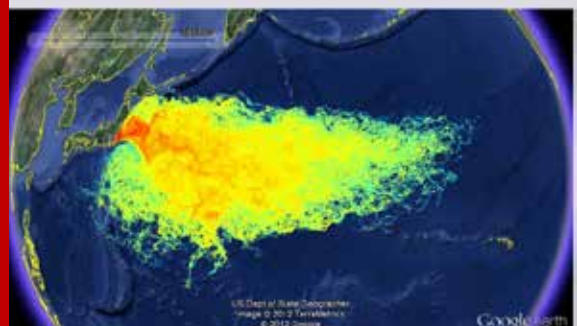
Jolee Mohr, with husband Robb and daughter

Contact: Osagie Obasogie
510-625-0819, ext 310

Troubling new revelations h
emerged this week in the d
an Illinois woman in a gene
therapy trial for arthritis,
prompting the Center for G
and Society to call on the fe
government to consider firm
regulatory action.

The death of 36-year-old Jo

Radioactive Seawater Impact Map (update: March 2012)



PRECAUTION: ACT ON WARNING TO REDUCE RISK IN ADVANCE OF HARMS

Y2K	US imposed standards and invested in infrastructure
Carcinogenicity	EPA “Delany Clause” ban on many potential carcinogens
GMO release	EU limits GMO field release
Pathogenic DNA elements	HHS DNA Screening Guidance (voluntary) + IGSC
Iran nuclear weapon	US-Israel attack Iran with Stuxnet and assassinations

11:59:59 31 DECEMBER 1999
12:00:00 01 JANUARY 2000

theguardian

Revealed: the lax laws that could allow assembly of deadly virus DNA

Urgent calls for regulation after Guardian buys part of smallpox genome through mail order

IGSC
international gene synthesis consortium™

IASB

PM AND SOX– LATE ADAPTATION

Portions of case from Kate Martin

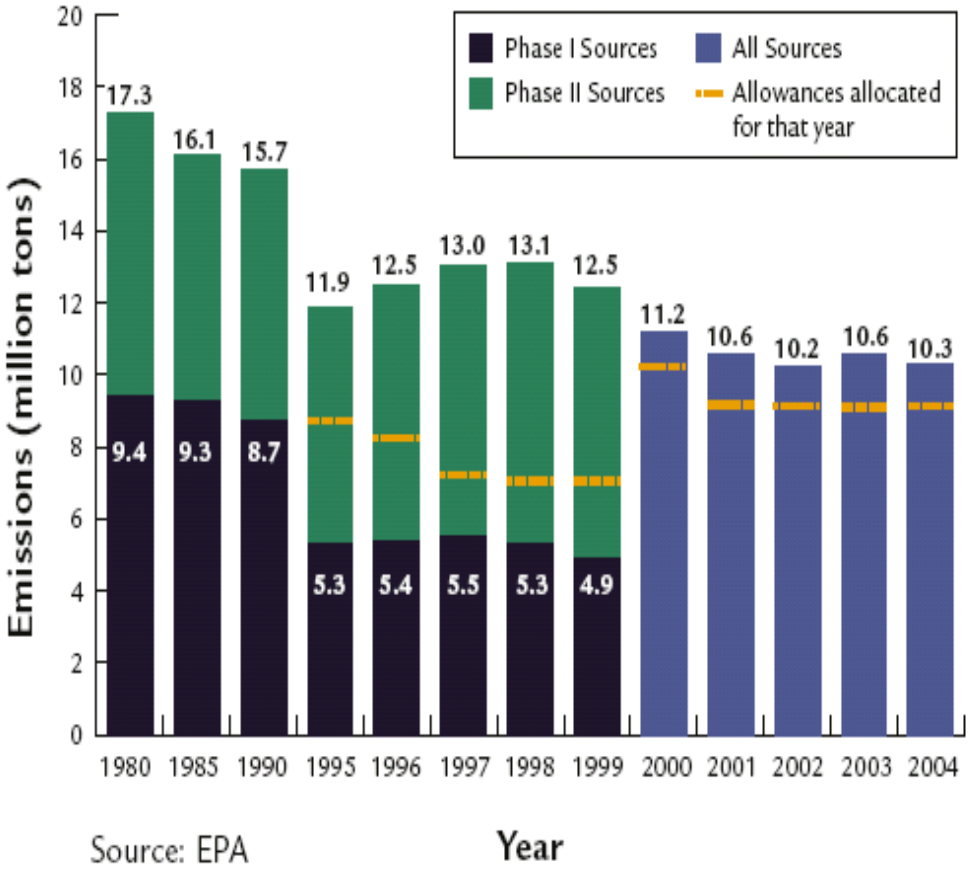
<u>Expected Costs of S02 Reduction</u>
1990 $550 per ton ± $250
2005 $250 per ton ± $ 50

<u>Expected Benefits of SO2 Reduction</u>
1990: acid rain benefits
2005: acid rain + PM health benefits

<u>Expected 2010 1:40 Cost:Benefit</u>
~ $3 billion annual cost
~ $120 billion annual benefit
For sulfur cuts from stationary sources

<u>Quotas and Targets</u>
New PM NAAQS need to be met by all.
Old SO2 NAAQS standard unchanged.

Figure 2: SO_2 Emissions under the Acid Rain Program



Source: EPA

Clean Air Interstate Rule will reduce SO2 by 70% from 2003 levels by 2015.
This is an additional 67% cut in SO2 from 2010 levels of the Acid Rain Program.

Health benefits of PM 2.5 cuts recognized in early 1990s…..changes coming in now.

Source: Figure 2 from US EPA, Acid Rain Program 2004 Progress Report.