Channeling Synthetic Biology Through "Solution-Focused Risk Assessment"

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Five Themes (the last two of which time permits only their assertion…):

1. Over the past 25 years, quantitative risk assessment (QRA) has become steadily more rigorous, accurate, transparent, and adaptable to a variety of problem areas.

2. However, QRA has often failed to be useful, because it has been detached from real deliberation about solutions.

3. We* are applying a "solution-focused risk assessment" framework to six case studies in SynBio– identifying human needs and comparing risks and benefits of alternative ways of meeting them.

* Finkel (U-Penn), Maynard, Bowman (U-Mich)

4. We need to do a better job estimating and communicating the benefits (including the risk reduction benefits) of SynBio products and processes.

5. We need to do a better job not being dismissive of risks/fears/ preferable alternatives. SynBio can't be the answer to every problem, or it may become the answer to no problems.

Regulation *versus* Freedom?

"… to shape those wise restraints that make us free"

--source unknown (to Google)

"Every generation of Americans needs to know that freedom exists not to do what you like but having the right to do what you ought."

--Pope John Paul II, Oct. 8, 1995

The Powerful Myth of Exaggerated Risk Assessment:

"The cumulative effect of following the upper-bound path, using a long series of conservative assumptions, can be monumental overestimates of health risks... The goal should be clear: Risk assessments should be as close to expected values… as the state of scientific knowledge permits."

- Albert Nichols and Richard Zeckhauser, "The Perils of Prudence," **Regulation,** Dec. 1986

"Using mouse terrorism, self-appointed 'environmentalists' and their allies in regulatory agencies … have been successful in dramatically inflating local, state, and federal budgets to underwrite … a far-reaching, taxpayer-supported, chemical witch hunt."

- Elizabeth Whelan, *Insight (*Washington *Times* magazine), 12/12/94

" 'Err on the safe side' scientific canons and default assumptions… may also help to convince environmentalists, press, and public that more should be done about known carcinogenic risks, even when those risks are tiny. Such public pressure, in turn, may encourage Congress… Congressional reaction provokes further public concern."

--Stephen Breyer, *Breaking the Vicious Circle*, 1993

Is "Humane Risk Analysis" a Contradiction in Terms?

"Right now risk assessment is used to answer the following sort of question: "How much of these 41 carcinogens can we give industry the right to dump into public waters without killing an unacceptable number of citizens?" Anyone who helps the state answer such an immoral question is essentially keeping the death camp trains running on time."

--*Rachel's Environment and Health Weekly, 11/7/96*

"To quiet the bereaved and turn this tragic toll into a form of publicly-sanctioned Russian Roulette, the government and industry are turning to a sham science called risk assessment."

--Andre Carothers, *E Magazine*, May 1991

Everything That Can Go Wrong Listed

FULLERTON, CA-A worldwide consortium of scientists, mathematicians, and philosophers is nearing the completion of the ambitious, decade-long project of cataloging everything that can go wrong, project leader Dr. Thomas R. Kress announced at a press conference Tuesday.

“We are mere weeks from finishing one of the most thorough and provocative scientific surveys of our time,” Kress said. “The catalog of every possible unfortunate scenario will complete the work of the ancient Phoenicians and the early Christian theologians. Soon, every hazardous possibility will be known to man.”

“And listed,” Kress added.

From *The Onion, 7/05*

run in stocking; nuclear annihilation of planet; phone system down; balloon floats away; glass eye falls out during speech; condom breaks; hairdresser quits; wolverine attacks child; White Stripes release bad album; lose $60 at bus stop; fatal heart attack; meat goes bad; floor collapses; tsunami; train wreck kills hundreds; computer crashes during lengthy download; Statue of Liberty falls over; grain elevator explodes; comet hits earth; ammo runs out; gored by moose; fan belt breaks on interstate; sour cream runs out; gassy; mother-in-law hates you; hamburger tastes charred; ignored by waiter; check gets lost in mail; $2 winning scratch-off washed with pants; get caught in middle of knife fight; humidity makes hair frizzy; cola explodes all over you; UPS package isn't for you; gas grill explodes all over you; neck breaks while clowning around; Livestrong bracelet gets caught in revolving door; everyone finds out you're a fraud; leg cramps up in middle of big game; strike out with bases loaded; boss catches you masturbating in your office; earth gets thrown off axis; plane gets hijacked; girlfriend's new friend cuter, funnier; pen dries out in middle of class; laptop battery loses charge; favorite bill gets vetoed; asshole paints swastika on Hillel center; oversleep on first day of work; neighborhood goes to seed; double-dutch jump rope; meeting with ambassador postponed; greeting card not a Hallmark; water doesn't taste like water at all; attempts to help poor perceived as racist; suffer second-degree burns trying to set toppled candle in jack-o-lantern upright; rescue operation fails when helicopter blade tips strike water tower; die of exposure after unknowingly taking more arduous path to summit; bite violently down on inside of cheek while eating sloppy joe; get shortchanged at charity bake sale; blind date repulsed by toenail parings on futon; mother throws out beloved old stuffed hippo; leg gets amputated by dredger chain; wrong backing-vocals tape played; final exam directions misinterpreted; real mother appears out of nowhere; friends, family learn the truth; drunk tattoo artist uses Dremel tool instead of needle; president roofied; lycanthropy turns out to be real; one of your legs grows four inches; pants stay unzipped all day; nosebleed unnoticed for first 10 minutes of wedding; batteries in remote control die; favorite song used in aerosol-cheese ad; toilet paper stuck to shoe when firemen rescues you; tacky plastic animals at gift

Questions Risk Assessors Ask:

- what can go wrong?
- how severe are the consequences?
- how likely is it to happen?
- how many people are at risk?

- how well do we know any of this?
- how relevant is the average risk for any actual person?
- do we have time to gather more information, and if so, what would be most valuable to know?

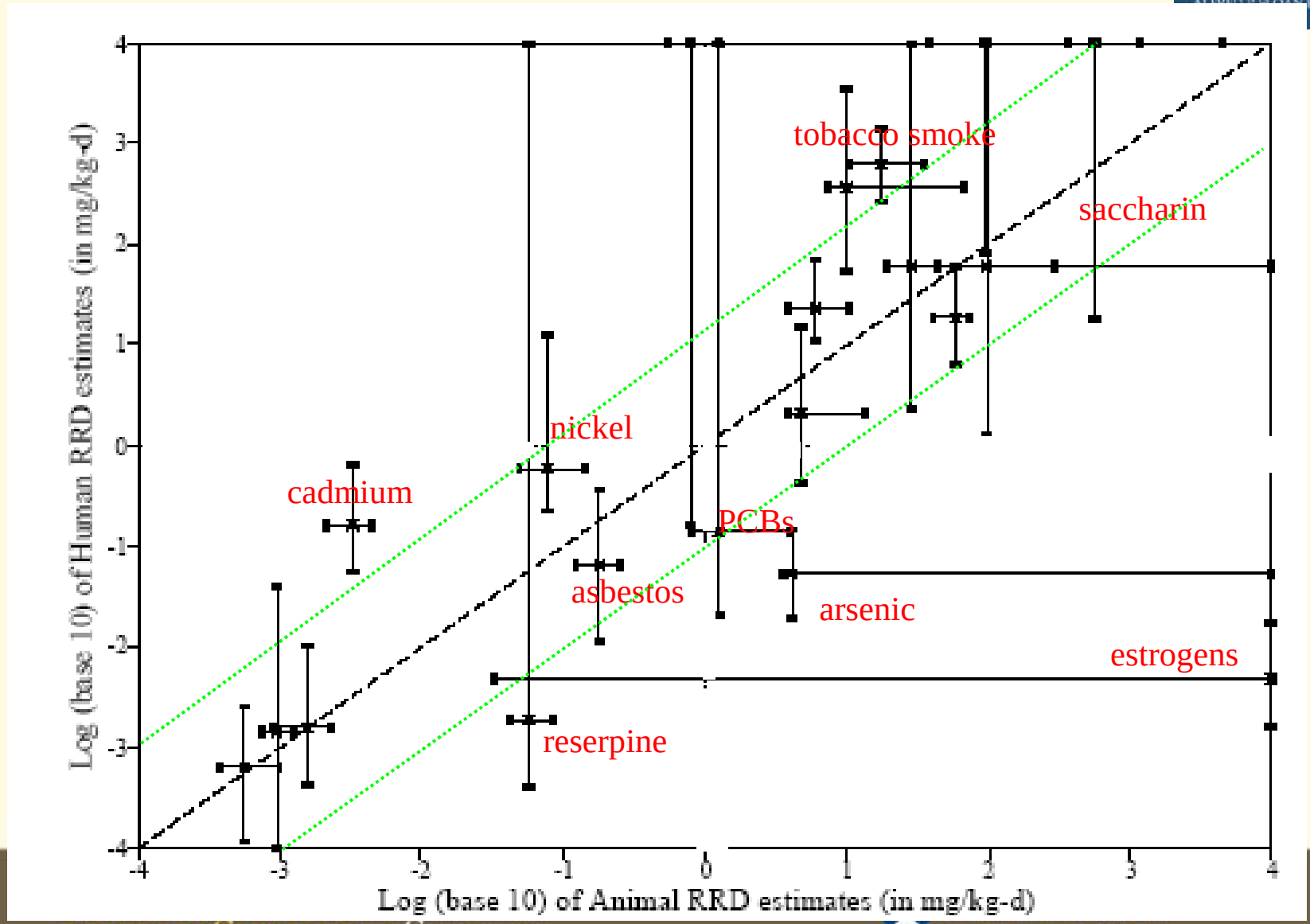
- how might we reduce the risk?
- at what cost?
- with what indirect benefits and/or unanticipated costs?

"I don't think anybody anticipated the breach of the levees. They did anticipate a serious storm."

-- President G.W. Bush, September 1, 2005 interview on ABC's "Good Morning America."

The design of the original levees, which dates to the 1960s, was based on rudimentary storm modeling that, it is now realized, might underestimate the threat of a potential hurricane. Even so, however, the levees were designed to withstand only forces associated with a fast-moving Category 3 hurricane. If a lingering Category 3 storm—or a stronger storm, say, Category 4 or 5—were to hit the city, much of New Orleans could find itself under more than 20 ft (6 m) of water.

-- Civil Engineering Magazine June 2003: "The Creeping Storm" (Greg Brouwer)


Log (base 10) of Human RRD estimates (in mg/kg-d)
Log (base 10) of Animal RRD estimates (in mg/kg-d)
4
3
2
1
0
-1
-2
-3
-4
-4
-3
-2
-1
0
1
2
3
4
tobacco smoke
saccharin
nickel
cadmium
PCBs
asbestos
arsenic
estrogens
reserpine

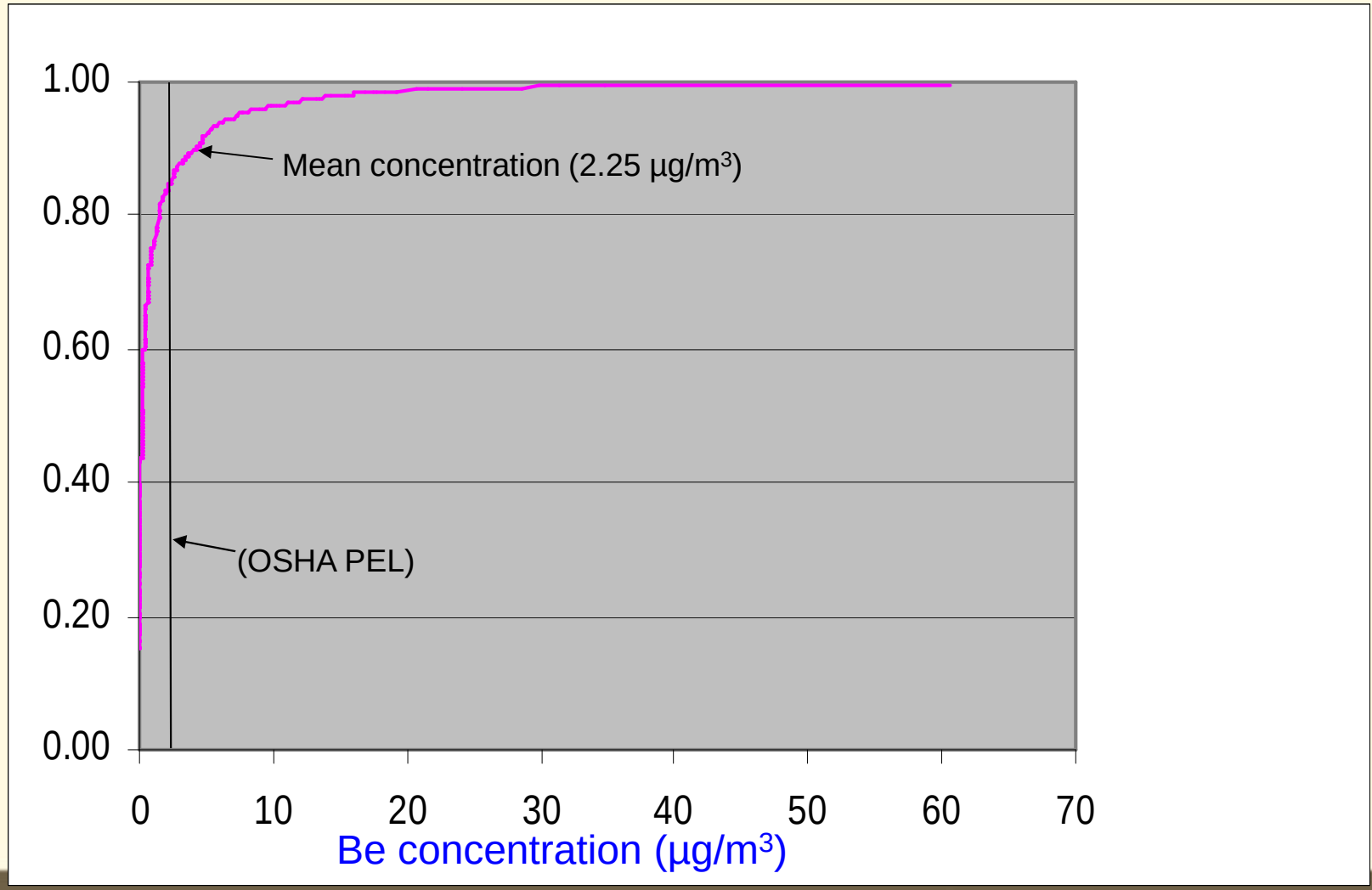
In 25 Years, I've Never Heard Anyone Acknowledge All Four of These Effects:

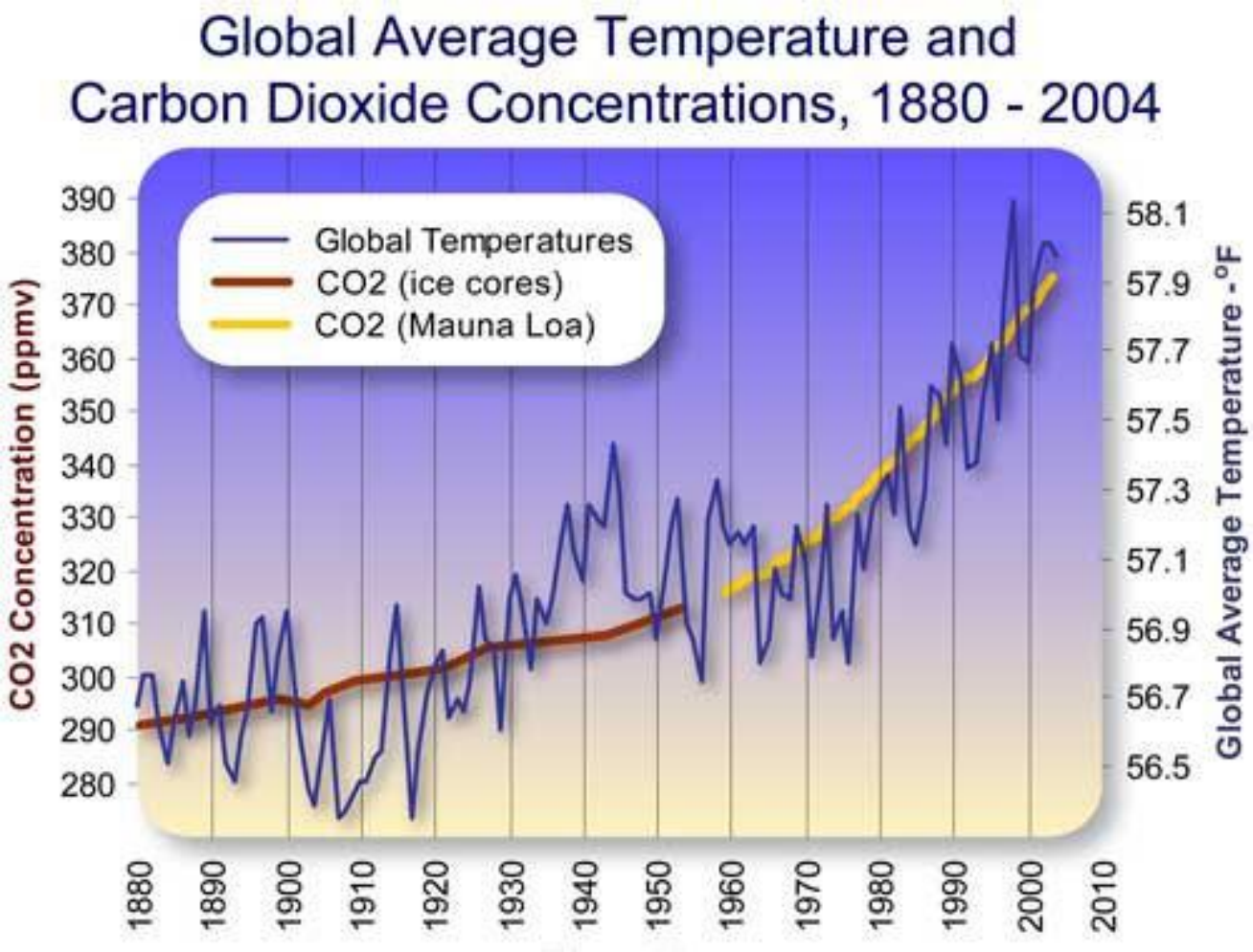
	Under-estimation	Over-estimation
BENEFITS	• above-average susceptibility • lab animals only tested from ages "2" to "70" • cumulative and aggregate risk • missing hazards • unquantified categories • NOAEL/100 may really be R=(0.05/1)	• linear at low doses • "porch potato" • simplistic mode of action • assume full compliance
COSTS	• surprise (cost overruns) • drag on managerial creativity • multiplier > 1 • regulation emboldens monopolists (asthma inhalers ex.)	• strategic "mis-estimation" • agency incentives • economies of scale • technological learning • count losses to losers, ignore gains to winners

Part 2: Three Problems with Contemporary Risk Assessment as a Risk Management Tool

(1): confusing aspiration with achievement.

Cumulative Distribution Function: Personal Samples for Beryllium in 1062 OSHA Inspections (Oct. 1992 – Oct. 2002)





(2): we sometimes do a lousy job heeding early (and mid, and late…) warnings… Therefore, an "early warning" system for SynBio risks may not be sufficient or even helpful…

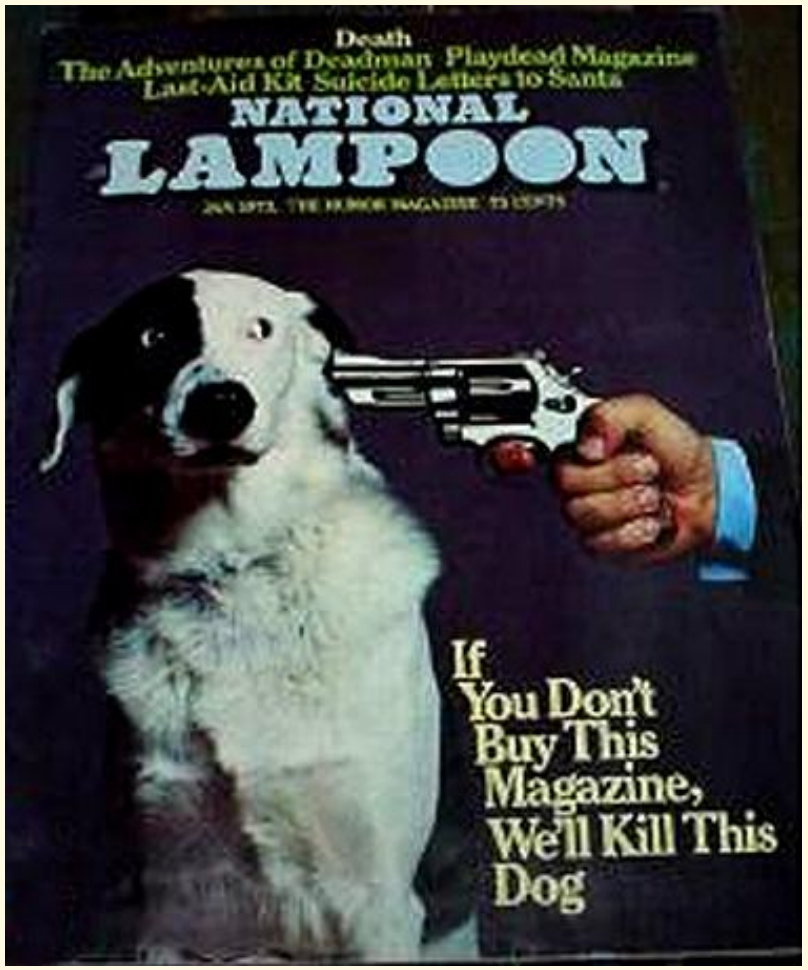
Graham-Wiener Typology, with Examples:

(3) Obliviousness to Risk-Risk tradeoffs

Population \ *Risk*	*Same Type*	*Different Type*
Same	Risk Offset stronger car roofs (reduce severity, increase (?) probability of a rollover)	Risk Substitution chlorination/cholera
Different	Risk Transfer intermedia pollutant transfers	Risk Transformation CAFE standards/ crashes

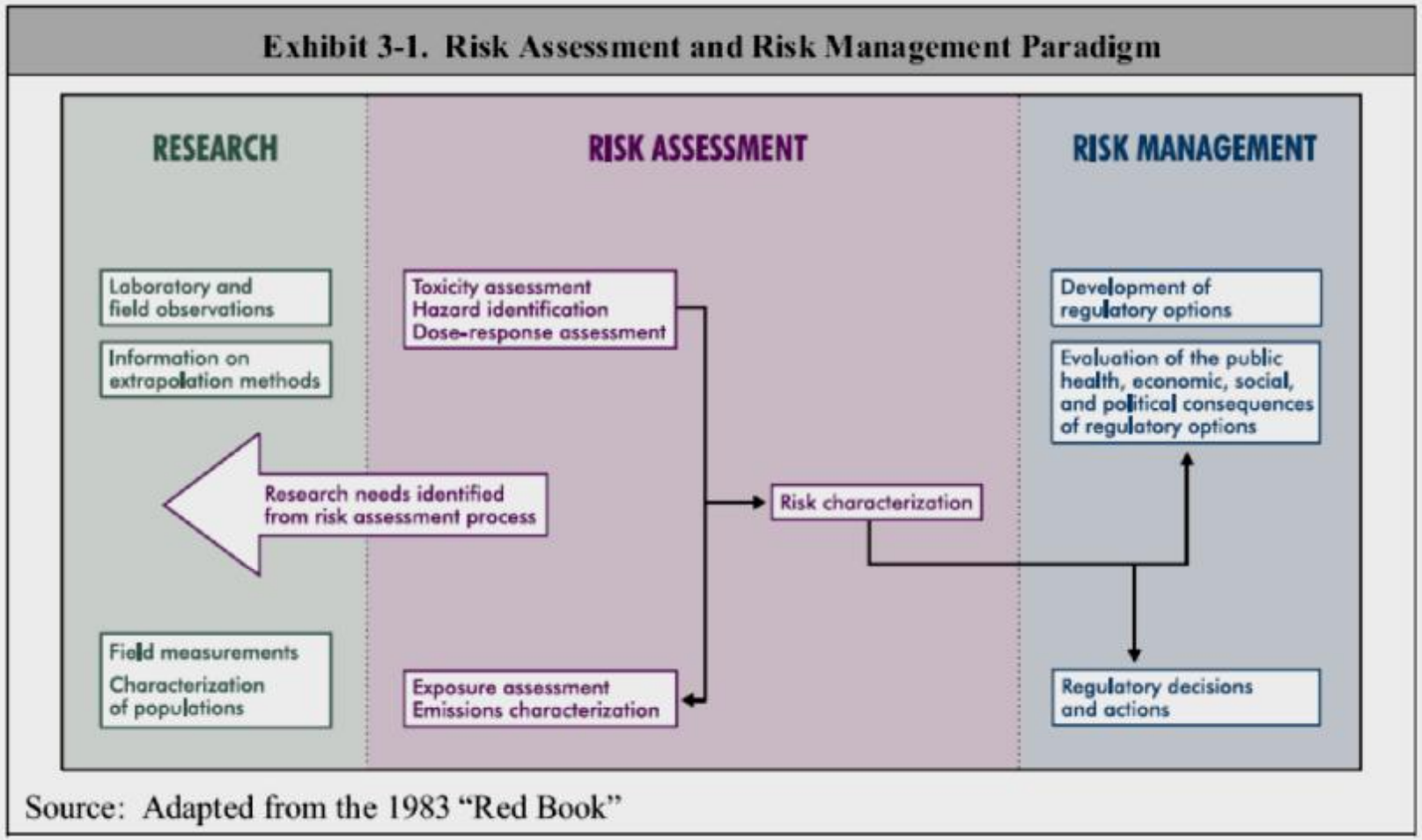
"If you don't allow us to spray methylene chloride all over our plants, we'll switch to a flammable substitute and play with matches"

(Jan. 1973)

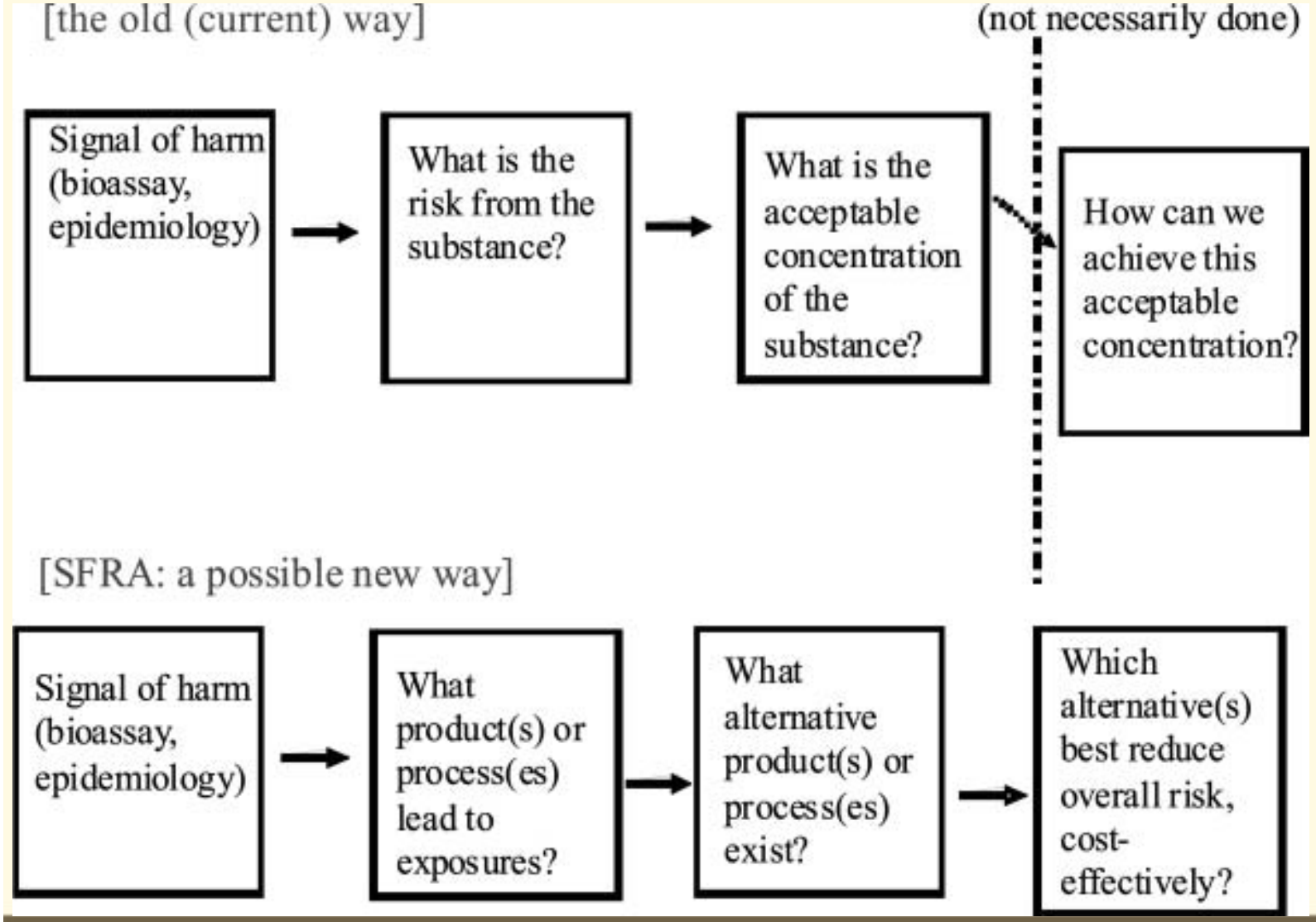


(46 accidents in U.S. involving acetone between 1990 and 2004– **none** in MC-using applications; overall rate has gone **down** since MC rule)

Problems with the traditional approach to risk-based decision-making:



"Solution-Focused Risk Assessment" (SFRA) as a new Synthesis:



SFRA-- Debts to Other Ideas

- Pioneers of decision-theoretic approach to environmental problems (Ralph Keeney, Bill Clemen, etc.)
- Cumulative risk assessment at EPA (Mike Callahan, Ken Sexton, etc.)
- Life-cycle analysis champions (e.g., SETAC)
- Technology options analysis (but herein with risk assessment embraced rather than marginalized)—Nick Ashford
- "Solving for Pattern"—Wendell Berry ("To define an agricultural problem as if it were solely a problem of agriculture—or solely a problem of production or technology or economics—is simply to misunderstand the problem, either inadvertently or deliberately... The whole problem must be solved, not just some handily identifiable and simplifiable aspect of it.")
- "TRIZ" (***Teoriya Resheniya Izobretatelskikh Zadatch***)—Russian (1946) "theory of solving inventors' problems"—see http://www.triz-journal.com/archives/1997/02/a/index.html for an example of "the ideal final result" for improving the lawnmower (grass engineered to stop growing when it reaches a 3" height) (with thanks to Mike Callahan for presenting it)
- Bjorn Lomborg—"Copenhagen Consensus" ranks solutions rather than problems; popularized via "How to Spend $50 Billion to Make the World a Better Place" (next slide)

Traditional risk assessment asks a narrow kind of question: “What allowable concentrations of each of 5 different chemicals should we allow in our plastic water bottles?” SFRA, in contrast, poses a more ambitious question: “How might we provide ready access to cold drinking water, perhaps with 29 billion FEWER bottles of any kind bought and thrown away each year?”

Case Study: Release of *A. aegypti* Mosquitoes Carrying Dominant Lethal Mutation

Function:

To reduce incidence, mortality, and morbidity from dengue fever

SynBio Risks:

- Short-term spike in disease transmission?
- Resistance to tetracycline dependency?
- Effects on species who prey on mosquitoes?

Alternatives and Their Risks:

- Chemical pesticides– ecological damage; human neurotox./cancer
- Netting– comparative lack of efficacy
- Repellants– toxicity; comparative lack of efficacy
- Vaccine against dengue– not yet available; cost?
- Intensive and constant environmental modification– cost
- Introduction of natural predators—ecosystem perturbations

Case Study: Production of Isoprene in *E. coli*

Function:

To produce consumer goods that are pliable, shock-absorbent, ductile, waterproof, etc., in a variety of applications

SynBio Risks:

- Limited control if accidental release
- Production of isoprene *in vivo* within humans
- Disruptive technology; livelihoods of thousands of workers

Alternatives and Their Risks:

- Natural rubber latex– energy-intensive; large environmental footprint, resource depletion
- Polyisoprene chemistry– higher cost (?– perhaps not over full life-cycle), but low/moderate risk
- Styrene-butadiene rubber– more toxic
- Recycled rubber– concerns about children's exposure

Other Case Studies (not discussed today):

- SynBio rodenticide (engineering viruses to engage in population control of rodents and small mammals; has a history of controversial use (cf. calicivirus in Australia)

- Algal ethanol (engineering algal cells to produce ethanol cheaply, efficiently, and with a high energy balance ratio

- Engineered GI flora for cholera prevention/reduction
- Environmental remediation of uranium contamination via bioprecipitation

TENTATIVE Themes of SFRA Case Studies:

- Other things equal, SynBio applications are more attractive when risks of alternatives are high, when status quo risk is large, or both;

- Government has a role to play in identifying products/processes with large environmental/health footprints (e.g., palm kernel oil), irrespective of profit potential for SynBio alternative;

- Bold questioning of the true human need(s) being fulfilled MAY prompt the search for an alternative that relies neither on SynBio nor on current risky technologies

Communicating SynBio Benefits:

The long-term horizon is important here: although the technology has some inherent ethical questions and start-up cost/unknown risk, maturation of the technology can help solve glaring issues in our modern economy and environment, including access to energy, disease control, and detection of harmful toxins. Existing technologies are helpful, but many are flawed in some way or another that SynBio could improve upon.

Some of the benefits of morally "unsettling" technologies are in principle incalculable, but must not be assumed to be small or morally unimportant. Although the risks of assisted reproductive technology are not yet wholly ruled out, the benefits include…

[If society allowed IVF to proceed, some enormous concepts were at stake: “the idea of the humanness of our human life and the meaning of our embodiment, our sexual being, and our relation to ancestors and descendants.”]

--Leon Kass, after the birth of Louise Brown in 1978

With Spokespeople Like These…

(… here I'm painting a broad-brush picture, using quotes from several recent general-interest books, of some amount of tone-deafness to the seriousness of the potential risks and the legitimacy of public reaction to them):

- "Few of the questions raised by synthetic genomics are truly new."
- "For me, a concern is 'bioerror': the fallout that could occur as the result of DNA manipulation by a non-scientifically trained biohacker or 'biopunk.' "
- "One can apply these principles [Isaac Asimov's "three laws of robotics"] equally to our efforts to alter the basic machinery of life by substituting 'synthetic life form' for 'robot.' "
- "It may be that current regulations will not be sufficient in the future, but they should be addressed at that point, not pre-emptively in a way that could prohibit progress."
- "We have answers for every question" [about the downsides of de-extinction], [he] told me. "We've been thinking about this for a long time."