Some recent headlines

Did FDR have Guillain-Barré syndrome?

Health effects of air pollution

Vioxx and cardiovascular disease

Statistics in the News

Nancy Reid

Universita’ de Padova

November 23, 2004
Some recent headlines

Did FDR have Guillain-Barré syndrome?

Health effects of air pollution

Vioxx and cardiovascular disease
Eating smart is good for your brain

Research is piling up that getting certain nutrients can help you concentrate and learn today, and ward off brain aging in the long run

By LESLIE BECK
Wednesday, September 8, 2004 - Page A17
News of the Week

Toxicology

Salmon Survey Stokes Debate About Farmed Fish

Salmon’s popularity has boomed in the past 2 decades as aquaculture has made salmon available year-round at low cost. The fish is a good source of protein, vitamin D, and heart-friendly fats. But fish farms have boosted less welcome ingredients: The largest survey yet of pollutants in salmon, reported on page 226, has found that farmed fish have higher levels of polychlorinated biphenyls (PCBs) and other organochlorine compounds than do wild-caught salmon. The source, as many researchers suspected, is the feed.

“This is a definitive study,” says nutritionist and toxicologist Miriam Jacobs of the University of Surrey, U.K., and Royal Veterinary College, London. “Further action has to be taken to reduce the contaminant levels in feed.” The authors argue that consuming more than one meal of farmed salmon per month may hike the risk of cancer. “The punch line is that eating the wrong kind of fish has real dangers,” says team member David Carpenter of the State University of New York, Albany, in Rensselaer.

Other experts say the risk is outweighed by the contaminant levels aren’t high enough to pose real dangers. “In my view, the study says we should be eating more farmed salmon,” says toxicologist Charles Santerre of Purdue University in West Lafayette, Indiana.

While nutritionists debate the study’s implications, consumers can use its data to try to select the cleanest fish possible. “I think we can begin to make informed choices about what kind of fish to eat,” says toxicologist Linda Birnbaum of the U.S. Environmental Protection Agency (EPA).

Seeing red. Farmed salmon has more PCBs than wild salmon, but scientists don’t agree on how much one should eat.

alyzed them for more than 50 contaminants. The greatest difference between farmed and wild salmon was in organochlorine compounds. Of the 14 of these chemicals measured, farmed salmon were more contaminated than wild ones. Farmers in Europe had the highest levels, followed closely by farmed salmon from North America. Whereas Chilean salmon were the cleanest, researchers also tested South American fish meal fed to the fish and found a similar pattern. Feeding salmon fish meal boosted growth and nutrition, but it also concentrated contaminants.

The team took a closer look at PCBs.
A new analysis of Franklin Delano Roosevelt’s symptoms suggests he might not have been stricken by polio but by Guillain-Barré syndrome.

In 1921, at the beginning of his political career, Roosevelt became feverish and developed paralysis, which started in his legs and moved up to his neck. Although he recovered partially, he remained permanently wheelchair-bound.

Immunological pediatrician Armond Goldman of the University of Texas Medical Branch in Galveston now says FDR’s symptoms are more concordant with Guillain-Barré syndrome, a bacterially induced autoimmune disease. For example,

Did FDR Have Guillain-Barré?

emerged as the more likely cause of his paralysis, they report in the 1 November Journal of Medical Biography.

“The result is interesting both historically and neurologically,” says neurologist Deborah Green of the University of Hawaii School of Medicine at Manoa. FDR’s misdiagnosis—if such it was—may have changed the course of history, because his affliction gave great momentum to efforts to develop a polio vaccine. But Green notes that “there’s no way to prove [a misdiagnosis] without testing the spinal cord fluid.” Neurologist H. Royden Jones of Harvard Medical School in Boston adds that the researchers could be wrong in assuming that “Guillain-Barré is the same now as it was back then.”

Getting Into a
Statistical error leaves pollution data up in the air

Jonathan Knight, San Francisco

An off-the-shelf statistics package has tripped up pollution researchers in North America and Europe who are studying the effects of airborne soot on human health.

A default setting that produced erroneous results went unchecked for years, despite significant statistical expertise in all of the groups. "It was already such standard software when we started using it, I didn't even question it," says Francesca Dominici, a public-health researcher at Johns Hopkins University in Baltimore, Maryland.

On 4 June, Dominici posted revised figures on her website after discovering that the error had doubled her group's estimate of the risk to health posed by particulates in the air. Two other groups that used the same tool, one in Canada and one in Greece, are now redoing their calculations.

The groups were looking for correlations between death rates and particulates in the air, which come mainly from diesel engines and power plants. Their data on air quality, hospitalizations and deaths from dozens of cities cover a seven-year period up to 1994.

Death rates vary throughout the year because of such factors as changes in temperature and disease outbreaks. To tease out the effects of particulates, the groups used a statistics program known as S-Plus.

S-Plus searches for correlations using an iterative process in which confounding effects are gradually peeled away. The default parameter in question determined how many times the procedure would iterate before stopping to produce a final result.

"For most applications the value is perfectly fine," says David Smith, product manager of Seattle-based Insightful, which sells S-Plus. Smith says that the Hopkins case was exceptional, but that users should always check whether changing the parameter affects the outcome, and adjust it if necessary. Smith says that Insightful will tighten the default value of the parameter — slowing the program slightly — on future releases of S-Plus.

Richard Burnett, a statistician with Health Canada in Ottawa, which is conducting a similar study, says that his group will probably revise its estimates of the impact of airborne soot on mortality downwards by 20–50%. The findings of a study run by a group at the University of Athens may also have to be adjusted, he says.

The health risk posed by particulates is a source of fierce environmental controversy in the United States, and the Bush administration is considering rules to restrict emissions. Opponents of tighter rules are likely to seize on the revisions as evidence that the research linking soot in the air to harmful effects on health is not to be trusted.
Data Revised on Soot in Air and Deaths

Scientists Lower Their Estimate of Risk From Bad-Air Days

BY ANDREW C. REVKIN

Revisiting their own data with new methods, scientists who conducted influential studies that linked sooty air pollution with higher death rates have lowered their estimate of the risk posed by bad-air days.

The findings do not challenge what is now a well-established link between air pollution and premature death. But the new analysis is highly likely to delay the final review of new regulations on small-particle pollution, officials of the Environmental Protection Agency said yesterday.

The review was projected to end, and the new rules to take effect, by the end of next year.

"This may clearly push it beyond that," a spokesman for the E.P.A., Joe Martyak, said last night.

The fine particles in question come mainly from power plants and diesel engines, and the proposed rules have been at the center of a long, political and public-relations battle between private environmental groups and power plant owner and vehicle manufacturers.

The researchers, at the Johns Hopkins University, have been distributing their new analysis to scientists who have used their old estimates to speak to public and political audiences.

New research may delay a review due next year on small-particle pollution.

kens biostatistics department, Dr. Scott L. Zeger, said other researchers who used the software, S-Plus, should check for similar problems. It is widely used for research in fields like pharmacology, genetics, molecular biology and stock-market forecasting, as well as serving as a mainstay of other environmental studies.

Dr. Zeger and Mr. Greenbaum stressed that the new findings did not overturn the basic link between soot and illness. They also pointed to the recent publication of other studies on the long-term effects of soot that do not use the same analytical tools.

Still, industry officials said the new findings called into question the validity of some research underlying the new federal standards.

"This study is really one of the ones creating the path for the future on air-quality regulation," said Allen Schaeffer, executive director of the Diesel Technology Forum.

The new results, Mr. Schaeffer said, show that "particle science is still evolving, and so are the analytical tools to look at it."

Scientists involved with the soot standard said that there was much other evidence that pointed to the dangers of soot but that the errors in the Hopkins work were still
Health officials examine Celebrex safety

TANYA TALAGA
HEALTH POLICY REPORTER

Federal health officials and the maker of Celebrex were scrambling yesterday to alleviate fears over the safety of the popular drug used to treat arthritis.
A published report suggested Celebrex, a product of Pfizer Canada Inc., is suspected of contributing to just over a dozen deaths and numerous heart and brain-related complications in Canada. The study is based on numbers obtained from an adverse drug reaction database, a surveillance tool Health Canada uses to monitor drugs in the marketplace. Dr. Maria Valois, Health Canada's director of marketed pharmaceuticals, told a group of journalists from across North America yesterday she was awaiting more information from Pfizer on the drug's safety in clinical trials and results from other countries.
She set a Nov. 18 deadline for the reports. Further action would depend on the material submitted, she said.
"It's still premature to conclude what intervention is required in this case," Valois said.
She said information pulled from the database shows Celebrex may "possibly" be connected to six deaths. "There is no proof the drug caused deaths. "Any health product has some benefit and some risk," Valois said.
Pfizer, the drug-maker Pfizer issued a statement from its New York headquarters saying the safety profile for Celebrex is well established by worldwide clinical trials. Millions have taken Celebrex since it was approved in 1998.
"The news report, based on voluntary spontaneous event reporting to Canadian health authorities, is misleading," the statement said in a statement. "The story is not supported by any clinical or epidemiological studies and has the potential to cause undue confusion among patients and physicians."
The database the numbers came from was information collected through voluntary reporting by doctors, he said.
Vioxx, the implosion of Merck, and aftershocks at the FDA

Today we publish results from a cumulative meta-analysis which show that the unacceptable cardiovascular risks of Vioxx (rofecoxib) were evident as early as 2000—a full 4 years before the drug was finally withdrawn from the market by its manufacturer, Merck. This discovery points to astonishing failures in Merck’s internal systems of post-marketing surveillance, as well as to lethal weaknesses in the US Food and Drug Administration’s regulatory oversight. The FDA’s approval of new drugs takes over safety evaluation is a serious flaw in FDA’s complex regulatory structure. In the case of Vioxx, FDA was urged to mandate further clinical safety testing after a 2001 analysis suggested a “clear-cut excess number of myocardial infarctions”. It did not do so. This refusal to engage with an issue of grave clinical concern illustrates the agency’s in-built paralysis, a predicament that has to be addressed through fundamental reform.
Merck Announces Voluntary Worldwide Withdrawal of VIOXX®

WHITEHOUSE STATION, N.J., Sept. 30, 2004—Merck & Co., Inc. today announced a voluntary worldwide withdrawal of VIOXX® (rofecoxib), its arthritis and acute pain medication. The company’s decision, which is effective immediately, is based on three-year data from a prospective, randomized, placebo-controlled clinical trial, APPROVe (Adenomatous Polyp Prevention on VIOXX) trial.

The trial, which is being stopped, was designed to evaluate the efficacy of VIOXX in preventing recurrence of colorectal polyps in patients with a history of colorectal adenomas. In this study, there was an increased relative risk for confirmed cardiovascular events, such as heart attack and stroke, beginning after 18 months of treatment in the patients taking VIOXX compared to those taking placebo. The results from the first 18 months of the APPROVe study did not show any increased risk of cardiovascular events on VIOXX, and in this respect, are similar to the results from the longer-term trial.
“What was the cause of Franklin Delano Roosevelt’s paralytic illness?” Goldman, et al. *J Medical Biography* 2003
Table 2. Diagnostic probabilities of eight key symptoms in Roosevelt’s paralytic illness appearing in Guillain–Bar
diomyelitis, tested by Bayesian analysis

<table>
<thead>
<tr>
<th>FDR’s case</th>
<th>GBS (prior probability 0.51)</th>
<th>Poliomyelitis (prior)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Symptom probability</td>
<td>Posterior probability</td>
</tr>
<tr>
<td>Paralysis ascends for 10–13 days</td>
<td>0.70</td>
<td>0.36</td>
</tr>
<tr>
<td>Facial paralysis</td>
<td>0.50</td>
<td>0.26</td>
</tr>
<tr>
<td>Bladder/bowel dysfunction for 14 days</td>
<td>0.50</td>
<td>0.26</td>
</tr>
<tr>
<td>Numbness/dysaesthesia</td>
<td>0.50</td>
<td>0.26</td>
</tr>
<tr>
<td>No meningismus</td>
<td>0.99</td>
<td>0.50</td>
</tr>
<tr>
<td>Fever</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Descending recovery from paralysis</td>
<td>0.70</td>
<td>0.36</td>
</tr>
<tr>
<td>Permanent paralysis</td>
<td>0.15</td>
<td>0.08</td>
</tr>
</tbody>
</table>

The derivation of the estimates of prior probabilities (relative frequencies of the diseases in FDR’s age range probabilities (the chance that a clinical feature occurred in a disease) of poliomyelitis and GBS is given in the considerations”. Posterior probabilities (the probability that FDR’s symptoms were due to a disease) are the symptom probabilities. Greater posterior probabilities are in bold type.
### Symptom

<table>
<thead>
<tr>
<th>Symptom</th>
<th>GBS Symptom Prob</th>
<th>GBS Posterior Prob</th>
<th>Polio Symptom Prob</th>
<th>Polio Posterior Prob</th>
</tr>
</thead>
<tbody>
<tr>
<td>ascending paralysis</td>
<td>0.70</td>
<td>0.36</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>facial paralysis</td>
<td>0.50</td>
<td>0.26</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>bladder/bowel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dysfunction</td>
<td>0.50</td>
<td>0.26</td>
<td>0.05</td>
<td>0.02</td>
</tr>
<tr>
<td>numbness</td>
<td>0.50</td>
<td>0.26</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>no meningismus</td>
<td>0.99</td>
<td>0.50</td>
<td>0.10</td>
<td>0.04</td>
</tr>
<tr>
<td>fever</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
<td>0.90</td>
<td>0.35</td>
</tr>
<tr>
<td>descending recovery</td>
<td>0.70</td>
<td>0.36</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>permanent paralysis</td>
<td>0.15</td>
<td>0.08</td>
<td>0.50</td>
<td>0.20</td>
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Prior probability 0.51 for GBS, 0.39 for polio
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Prior probability 0.51 for GBS, 0.39 for polio
Bayes theorem

“using a retrospective analytical technique devised by the Reverend Thomas Bayes (1702–1761) and published in 1763, two years after his death”

\[ Pr(\text{disease} \mid \text{symptom}) \propto Pr(\text{symptom} \mid \text{disease}) Pr(\text{disease}) \]

Likelihood Prior

each symptom treated separately, for example

\[ Pr(\text{GBS} \mid \text{facial paralysis}) \propto Pr(\text{facial paralysis} \mid \text{GBS}) Pr(\text{GBS}) \]

\[ 0.26 \times 0.50 \times 0.51 \]

\[ Pr(\text{Polio} \mid \text{facial paralysis}) \propto Pr(\text{facial paralysis} \mid \text{polio}) Pr(\text{polio}) \]

\[ 0.02 \times 0.02 \times 0.39 \]
**GBS**

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<tr>
<th>Symptom</th>
<th>Symptom Prob</th>
<th>Posterior Prob</th>
</tr>
</thead>
<tbody>
<tr>
<td>ascending paralysis</td>
<td>0.70</td>
<td>0.98</td>
</tr>
<tr>
<td>facial paralysis</td>
<td>0.50</td>
<td>0.97</td>
</tr>
<tr>
<td>bladder/bowel dysfunction</td>
<td>0.50</td>
<td>0.93</td>
</tr>
<tr>
<td>numbness</td>
<td>0.50</td>
<td>0.99</td>
</tr>
<tr>
<td>no meningismus</td>
<td>0.99</td>
<td>0.93</td>
</tr>
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<td>fever</td>
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<td>0.01</td>
</tr>
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</tr>
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**Polio**

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<tbody>
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<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>facial paralysis</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>bladder/bowel dysfunction</td>
<td>0.02</td>
<td>0.07</td>
</tr>
<tr>
<td>numbness</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>no meningismus</td>
<td>0.10</td>
<td>0.07</td>
</tr>
<tr>
<td>fever</td>
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<td>0.99</td>
</tr>
<tr>
<td>descending recovery</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>permanent paralysis</td>
<td>0.50</td>
<td>0.72</td>
</tr>
</tbody>
</table>

Prior probability 0.56 for GBS, 0.44 for polio

"Symptom Probability" = Likelihood = Pr(symptom | disease) estimated from literature; better to estimate from confirmed cases?
Table 1. Clinical features of Franklin D Roosevelt’s case compared with those of Guillain–Barré syndrome (GBS) and poliomyelitis.

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Roosevelt’s case</th>
<th>GBS</th>
<th>Poliomyelitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>39 years</td>
<td>Mainly adults</td>
<td>Mainly young</td>
</tr>
<tr>
<td>Flaccid paralysis</td>
<td>Symmetric, ascending</td>
<td>Symmetric, ascending</td>
<td>Asymmetric</td>
</tr>
<tr>
<td>Progress of paralysis</td>
<td>10–13 days</td>
<td>10–14 days</td>
<td>3–5 days</td>
</tr>
<tr>
<td>Facial paralysis</td>
<td>Present</td>
<td>Common, bilateral</td>
<td>Rare, save in</td>
</tr>
<tr>
<td>Bladder/bowel dysfunction</td>
<td>14 days</td>
<td>7–14 days</td>
<td>1–3 days</td>
</tr>
<tr>
<td>Numbness</td>
<td>Present</td>
<td>Common</td>
<td>Absent</td>
</tr>
<tr>
<td>Dysaesthesia</td>
<td>Protracted</td>
<td>Protracted</td>
<td>Absent</td>
</tr>
<tr>
<td>Meningismus</td>
<td>Absent</td>
<td>Absent</td>
<td>Common</td>
</tr>
<tr>
<td>Fever</td>
<td>Present</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Recovery from paralysis</td>
<td>Symmetric, descending</td>
<td>Symmetric, descending</td>
<td>Asymmetric</td>
</tr>
<tr>
<td>Permanent paralysis</td>
<td>Symmetric</td>
<td>In about 15% of cases</td>
<td>In about 50%</td>
</tr>
</tbody>
</table>

\(^{a}\)The clinical features of poliomyelitis and GBS have been drawn from many past publications.\(^{36-45}\)
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The review was projected to end, and the new rules to take effect, by the end of next year.

"This may clearly push it beyond that," a spokesman for the E.P.A., Joe Martyak, said last night.

The fine particles in question come mainly from power plants and diesel engines, and the proposed rules have been at the center of a long legal, political and public-relations battle between private environmental groups and power plant owner and vehicle manufacturers.

The researchers, at the Johns Hopkins University, have been distributing their new analysis to scientists and government officials by fax and e-mail. Yesterday, they set up a Web site, biosun1.biostat.jhsp.edu/~ldominic/research.html, that details their new findings.

"This is a very important finding," said Daniel V. Health, a statistician at the National Cancer Institute. "It's going to shake a lot of assumptions about the relationship between particle pollution and health effects."

The revised risk estimate was made by two of the researchers who published the earlier research, and Dr. Joseph M. Spengler, a leading expert on the health effects of air pollution at Harvard University.

The scientists found that the risk of death increases about 2 percent for each 10 micrograms per cubic meter of soot.

They say they have found a "very strong" relationship between the two, and that there is a greater risk of death from other causes.

New research may delay a review due next year on small-particle pollution.
“the new analysis is highly likely to delay the final review of new regulations on small-particle pollution”

“industry officials said the new findings called into question the validity of some research underlying the new federal standards”

“It certainly brings into question the precision of the data’, said Dr. Jane Q. Koenig”

“The health risk posed by particulates is a source of fierce environmental controversy in the United States”

“Opponents of tighter rules are likely to seize on the revisions as evidence that the research linking soot in the air to harmful effects on health is not to be trusted”

“A default setting that produced erroneous results went unchecked for years, despite significant statistical expertise in all the groups”
“The findings do not challenge what is now a well established link between air pollution and premature death”

“The work has been published for several years in a variety of the leading journals like the New England Journal of Medicine and the American Journal of Epidemiology”

“The project, the National Morbidity, Mortality and Air Pollution Study, was given extra weight by policy makers because of the reputation of the Health Effects Institute and the Johns Hopkins group”

Not as well known that the effect was also discovered at Health Canada, by Tim Ramsay and Rick Burnett

Their work also drew attention to the incorrect calculation of standard errors in the gam software

Original estimate 0.41% increase in mortality rate associated with increase of $10 \mu g/m^3$ increase in $PM_{10}$.

Revised estimate 0.22%.

These are small effects; perhaps 1-2 additional deaths per year in Padova
The data

- daily mortality counts from NCHS (National Center for Health Statistics) 1987-1994
- hourly temperature and dewpoint data from National Climatic data Center
- data on pollutants $PM_{10}$, $O_3$, $CO$, $SO_2$, $NO_2$ from EPA

The model

- $Y_t$ mortality rate on day $t$ follows a Poisson distribution with mean $\mu_t$
- $\log \mu_t$ depends on a number of inputs: pollution on day $t - 1$, age and size of population, weather, day of the week, time
- effect of pollution is linear, effect of confounders is ‘smooth’
- fit the same model for each city, pool effect estimates
... the model

\[ \log \mu_{at} = \beta X_{t-1} + \gamma DOW + S_1(t, 7) + S_2(temp_0, 6) + S_3(temp_{1-3}, 6) + S_4(dew_0, 3) + S_5(dew_{1-3}, 3) + \alpha_a + S_6(a(t, 8)) \]

- \(a\) indexes age groups, \(t\) time (days)
- \(S(z, 8)\) is a non-specified, but smooth, function of \(z\) with 8 ‘degrees of freedom’, can think of it as a spline with a pre-specified number of knots. Large df means wiggly function, 1 df is linear
- mortality rates change with season, weather, changes in health status, ...
- Is there anything left for pollution?
Population studies

- use pollution measurements at monitoring stations
- use city-wide mortality rates
- use relatively crude measures of weather
- are ‘ecological’ studies
- what is the real dose to an individual?
- are there ‘effect modifiers’ (e.g. average income, average age)
- what about micro-climates?
- what are the mechanisms?
- (note these are acute, not chronic, effects)
- (note gaseous pollutants)
Bradford-Hill criteria for causality

- consistency of evidence ("coherence")
- biological plausibility
- temporality
- dose response

Rothman and Greenland: *Modern Epidemiology*
Merck Announces Voluntary Worldwide Withdrawal of VIOXX®

WHITEHOUSE STATION, N.J., Sept. 30, 2004—Merck & Co., Inc. today announced a voluntary worldwide withdrawal of VIOXX® (rofecoxib), its arthritis and acute pain medication. The company’s decision, which is effective immediately, is based on three-year data from a prospective, randomized, placebo-controlled clinical trial (APPROVe [Adenomatous Polyp Prevention on VIOXX] trial).

The trial, which is being stopped, was designed to evaluate the efficacy of VIOXX in preventing recurrence of colorectal polyps in patients with a history of colorectal adenomas. In this study, there was an increased relative risk for confirmed cardiovascular events, such as heart attack and stroke, beginning after 18 months of treatment in the patients taking VIOXX compared to those taking placebo. The results of the first 18 months of the APPROVe study did not show any increased risk of confirmed cardiovascular events on VIOXX, and in this respect, are similar to the results of the entire APPROVe trial.
Pfizer Affirms Celebrex Safety

NEW YORK, September 30, 2004—In response to Merck & Co.’s announcement today of the worldwide withdrawal of its COX-2 medicine Vioxx, Pfizer Inc issued the following statement:

Over 27 million patients in the United States have been prescribed Celebrex (celecoxib), which was approved by the U.S. Food and Drug Administration in 1998.
Health officials examine Celebrex safety

TANYA TALAGA  
HEALTH POLICY REPORTER

Federal health officials and the maker of Celebrex were scrambling yesterday to alleviate fears over the safety of the popular drug used to treat arthritis. A published report suggested Celebrex, a product of Pfizer Canada Inc., is suspected of contributing to just over a dozen deaths and numerous heart and brain-related complications in Canada. The reports, based on numbers obtained from an adverse drug reaction database, a surveillance tool Health Canada uses to monitor drugs in the marketplace. Dr. Maria Valois, Health Canada's director of marketed pharmaceuticals, told a group of journalists from across North America yesterday she was awaiting more information from Pfizer on the drug's safety from clinical trials and results from other countries.

She set a Nov. 18 deadline for the reports. Further action would depend on the material submitted, she said. "It's still premature to conclude what intervention is required in this case," Valois said.

She said information pulled from the database shows Celebrex may "possibly" be connected to six deaths. "There is no proof the drug caused deaths. "Any health product has some benefit and some risk," Valois said. Drug-maker Pfizer issued a statement from its New York headquarters saying the safety profile for Celebrex is supported by worldwide clinical trials. Millions have taken Celebrex since it was approved in 1998.

"The news report, based on voluntary spontaneous event reporting to Canadian health authorities, is misleading," said in a statement. "The story is not supported by any clinical or epidemiological studies and has the potential to undue confusion among patients and physicians."

The database the numbers came from uses information collected through voluntary reporting by doctors, health professionals and patients.
Vioxx, the implosion of Merck, and aftershocks at the FDA

Today we publish results from a cumulative meta-analysis which show that the unacceptable cardiovascular risks of Vioxx (rofecoxib) were evident as early as 2000—a full 4 years before the drug was finally withdrawn from the market by its manufacturer, Merck. This discovery points to astonishing failures in Merck’s internal systems of post-marketing surveillance, as well as to lethal weaknesses in the US Food and Drug Administration’s regulatory oversight. In a recent Editorial, we commended Merck for acting promptly in the face of new findings about the safety of Vioxx.1 Our praise was premature. The evidence showing that Vioxx caused significant adverse events was apparent well before data from the APPROVe trial triggered Merck’s overdue intervention. This week’s report by Peter Jüni and colleagues will add significant weight to ongoing litigation against Merck by patients who believe they were harmed by this drug.

These findings also come in the wake of new disclosures that suggest Merck was indeed fully aware of Vioxx’s potential risks by 2000. Investigations by the Wall Street Journal2 have revealed e-mails that confirm Merck executives’ knowledge of their drug’s adverse cardiovascular profile—the risk was “clearly there”, according to one senior researcher. Merck’s marketing literature included a document intended for its sales representatives which discussed how to respond to questions about Vioxx—it was labelled “Dodge Ball Vioxx”. Given this disturbing contradiction—Merck’s own understanding of Vioxx’s true risk profile and its attempt to gloss over these risks in their public statements at the time—it is hard to see how Merck’s chief executive officer, Raymond C. Gilmartin, can continue in the role of being the FDA’s most important constituency.

The licensing of Vioxx and its continued use in the face of overwhelming evidence of its adverse cardiovascular profile set a dangerous precedent, encouraging new drugs to be approved without rigorous safety evaluation. This is a serious flaw in FDA’s complex regulatory structure. In the case of Vioxx, FDA was urged to mandate further clinical safety testing after a 2001 analysis suggested a “clear-cut excess number of myocardial infarctions”.3 It did not do so. This refusal to engage with an issue of grave clinical concern illustrates the agency’s in-built paralysis, a predicament that has to be addressed through fundamental organisational reform.

On Nov 2, 2004, the FDA tried to shore up its tarnished reputation by posting on its website an early version of a recently completed observational study into the safety of Vioxx. The report comes with a warning that it has “not been fully evaluated by the FDA and may not reflect the official views of the agency”. The FDA investigators estimate that over 27 000 excess cases of acute myocardial infarction and sudden cardiac death occurred in the USA between 1999 and 2003. “These cases”, they write, “would have been avoided had celecoxib been used instead of rofecoxib”. This study is presently under review at The Lancet. It is unclear why the FDA could not have waited for the fully evaluated report to have been scrutinised, revised, and published according to the norms of scientific peer review. Bypassing independent peer review smacks of panic in the FDA, which is under intense reputational pressure. And yet its decision to try to undermine the integrity of this work again shows that the agency’s senior management is more concerned with external appearance than rigorous science.

The licensing of Vioxx and its continued use in the face of overwhelming evidence of its adverse cardiovascular profile set a dangerous...
“this week’s report by Peter Jüni and colleagues will add significant weight to ongoing litigation against Merck”

“it is hard to see how Merck’s chief executive officer, Raymond Gilmartin, can retain the confidence of the public”

“The inherent precedence that licensing of new drugs takes over safety evaluation is a serious flaw in FDA’s complex regulatory structure”

“Merck’s likely litigation bill is put at between US "$10 and $15 billion”

Market value of Merck dropped to $15 billion from $30 billion following the announcement
Some recent headlines

- Did FDR have Guillain-Barré syndrome?
- Health effects of air pollution
- Vioxx and cardiovascular disease

meta-analysis

![Meta-analysis of randomised trials comparing rofecoxib with control](image)

Figure 2: Meta-analysis of randomised trials comparing rofecoxib with control
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Cumulative meta-analysis
Merck fights back

Response to Article by Juni et al. Published in The Lancet on Nov. 5

In an article that appeared in Lancet on Nov. 5, 2004, Juni et al. present a meta-analysis of rofecoxib data and conclude that an increased risk for cardiovascular events on rofecoxib was apparent in the year 2000. These conclusions are based on an analysis that violates the basic principle of meta-analyses to combine “like with like”. In this analysis, the authors combined data from studies with 3 different kinds of comparators. The conclusion by Juni et al. of a difference in myocardial infarction (MI) risk for rofecoxib, regardless of comparator, is driven by the difference between rofecoxib and a single comparator, naproxen, especially by the results of VIGOR (Bombardier C, et al. N Engl J Med 2000; 343: 1520–28). The data in this article had already been included in the first rofecoxib pooled analysis published in 2001 by Konstam et al. (Circulation 2001;104:2280) and again in 2003 (Am Heart J 2003;146:591). These pooled analyses demonstrated a difference in cardiovascular risk between rofecoxib and naproxen but not between rofecoxib and non-naproxen NSAIDs or placebo.
Merck fights back (www.merck.com)

▶ “These conclusions are based on an analysis that violates the basic principle of meta-analyses”

▶ “The authors’ analysis by comparator confirms that the only statistically significant difference in MI risk was between rofecoxib [vioxx] and naproxen”

▶ “This use of an underpowered statistical test ... is scientifically inappropriate”

▶ “This selective omission of a large placebo-controlled data sets available in 2001 ... limits the authors conclusions”

▶ “Our business prospects are strong and we are well prepared to address the challenges posed by the withdrawal of VIOXX. We have a strong balance sheet, with cash and reserves that well exceed debt.”
On a more positive note (Jüni et al.)

▶ “The inclusion of an independent endpoints committee should be the rule...”

▶ “Possible explanations for these discrepant results include: confounding by trial, inadequately pooling individual patients’ data, use of composite cv endpoints

▶ “the FDA and other drug licensing authorities should ... identify and remove the obstacles to making continuously updated summary information available”

▶ “we should resist being seduced by mechanisms, we should suspend our beliefs, and allow healthy scepticism when interpreting data”

▶ “we can never be sure that we know all there is to know about mechanisms”
Statistics in the News

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