

# Foundations for the Illusion of Certainty Pertaining to Health Risks and Benefits

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# Motivation

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- ❖ Health benefits and risks are part of our everyday language
- ❖ They get extensive media coverage
- ❖ Examples for environmental contaminants
  - Evidence confirms that PCBs in the Hudson River have tripled the likelihood that certain species of fish will not be able to reproduce in 8 years
  - People exposed to elevated radon levels in indoor air have a dramatically increased risk of getting lung cancer
  - Individuals have a 1 in 100,000 increased risk of getting cancer due to the presence of arsenic in their well water
  - An additional 2 out of 1,000,000 individuals will die from a lifetime exposure to benzene, chloroform, and dioxin emissions from the two California pulp mills
  - Chromium contamination in sediments significantly increases the risk of toxicity to aquatic organisms

# Motivation (continued)

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- ❖ Examples from public health and medical groups
  - Screening tests for prostate cancer (PSA) can determine which men are at a higher risk for getting this deadly disease
  - Mammograms are recommended for women 40 and older for breast cancer screening
  - Eating grilled meat increases your risk of dying from cancer
  - People with elevated blood serum cholesterol levels have a 100% greater risk of getting atherosclerosis and heart disease compared to individuals with normal cholesterol
  - Individuals taking statins to lower their blood serum cholesterol levels benefit by having fewer heart attacks
  - Researchers have found an increased risk of heart attack or stroke for people taking Vioxx™

# Motivation (continued)

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- ❖ Are these statements accurate? Meaningful?
- ❖ We seek medical intervention and make dramatic lifestyle changes hoping they will provide benefits
- ❖ Managing environmental contaminants involves costs
- ❖ Benefit and risk statements tend to be presented as if they are authoritative, definitive, and based on clear and unequivocal evidence
- ❖ Hence our book: *The Illusion of Certainty: Health Benefits and Risks* (Springer 2007)
  - We explain that the information provided to us on health risks and benefits--by drug companies, the media, and other organizations--often constitutes misinformation
  - Our goal is to empower people to make well informed decisions about health benefits and risks

# Cause and Effect vs. Risk Factors

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- ❖ For some ailments, the relationship between the cause and effect is well established
  - HIV is the cause, AIDS is the effect
  - *Plasmodium* is the cause, malaria is the effect
- ❖ When there is no established direct cause and effect, we rely on a risk factor approach
  - A risk factor is based on an association but has not been proven to cause an event or disease
  - Risk factors are used to understand health problems like coronary heart disease, cancer, stroke, and diabetes
- ❖ Medical interventions are much more certain when there is a cause and effect

# How are Health Risks and Benefits Communicated?

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- ❖ Examples from the media
  - “Study Shows 43% More Heart Attacks with Avandia” (Avandia is a popular drug for diabetes)
  - “H.R.T. Leads to 10% Higher Risk for Heart Attacks”
  - “Lipitor Lowers Your Cholesterol by 30% to 60%” (Lipitor is a statin)
- ❖ The values reported are nearly always relative values (percent differences)
- ❖ The values are reported as “certain” values. Any sense of uncertainty in the numbers is normally lost.

# Absolute Risk and ARR

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- ❖ **Absolute risk** is your risk of developing a disease over a specified period of time
- ❖ **Absolute risk** reflects the number of people who will be harmed compared to the total number of people being considered.
  - If 6 out of 100 get a disease and die, the A.R. is  $6/100$  or 0.06 or 6%
- ❖ **Absolute Risk Reduction** is the difference between two absolute risks in two groups
  - In the above example, if people take a drug and only 4 out of 100 get the disease and die, the ARR is  $6\% - 4\% = 2\%$ . Two lives are saved out of 100
- ❖ **ARR** compares the number of people who will benefit from intervention to the total number of people being considered

# Relative Risk

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- ❖ **Relative risks** are based on the ratio of two absolute risk numbers. When using relative risks, the absolute risk levels for the experimental and control groups are not known.
  - If taking a new drug reduces the number of disease deaths from 6 out of 100 (6%) to 4 out of 100 (4%), then the relative risk difference is 33% because 4% is 33% less than 6%. The absolute risk difference is 2% (6% - 4%).
- ❖ 33% sounds much better than 2%

# Making Decisions

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- ❖ Absolute risks/benefits and ARR are essential to make informed decisions about what to do
  - Baseball score analogy to illustrate how relative numbers can be misleading
  - Mosquitoes in a room
  - Increased lightning from global warming is not likely to keep us indoors
  - Buying two lottery tickets instead of one still gives you a small chance of winning
  - Doubling a trivial risk is still a trivial risk

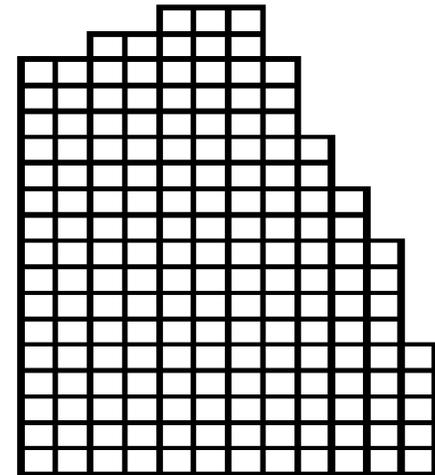
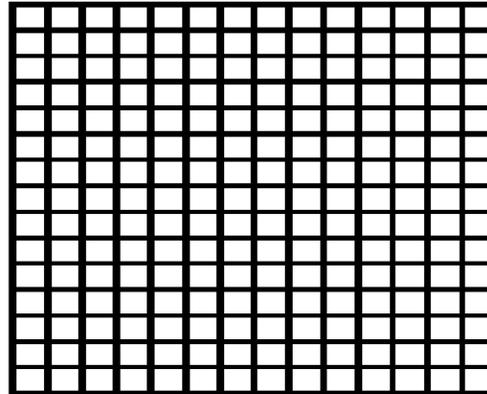
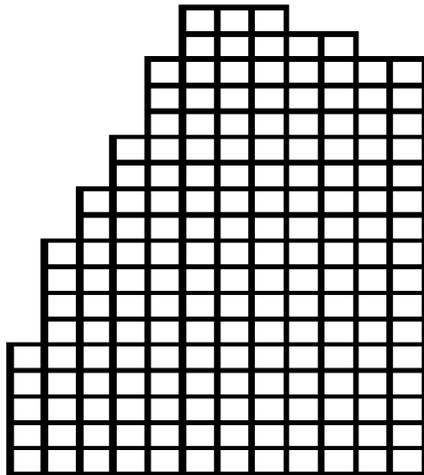
# Visualizing Health Benefits and Risks

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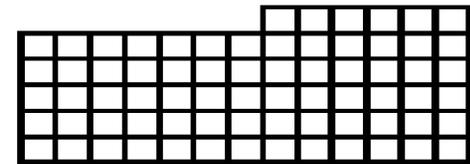
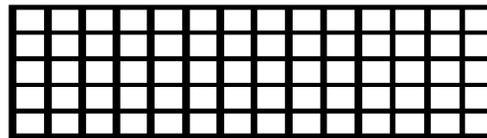
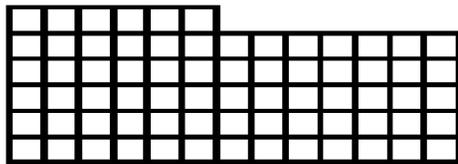
- ❖ Need a simple format that presents the uncertainty, risks, and benefits associated with screening tests, environmental risk assessments, and drugs for treating chronic ailments
- ❖ Work with absolute numbers
- ❖ We developed a theater seating chart to communicate risks and benefits
  - Most of us are familiar with the crowd in a typical theater as a graphic illustration of a population grouping

# Risk Characterization Theater (RCT)

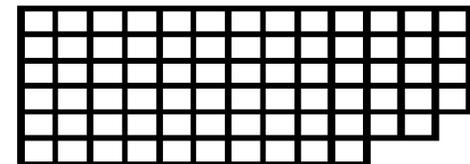
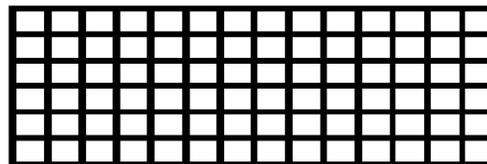
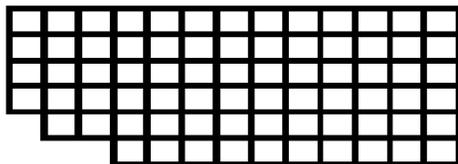
**Stage**



**Orchestra**



**Front Mezzanine**



**Rear Mezzanine**

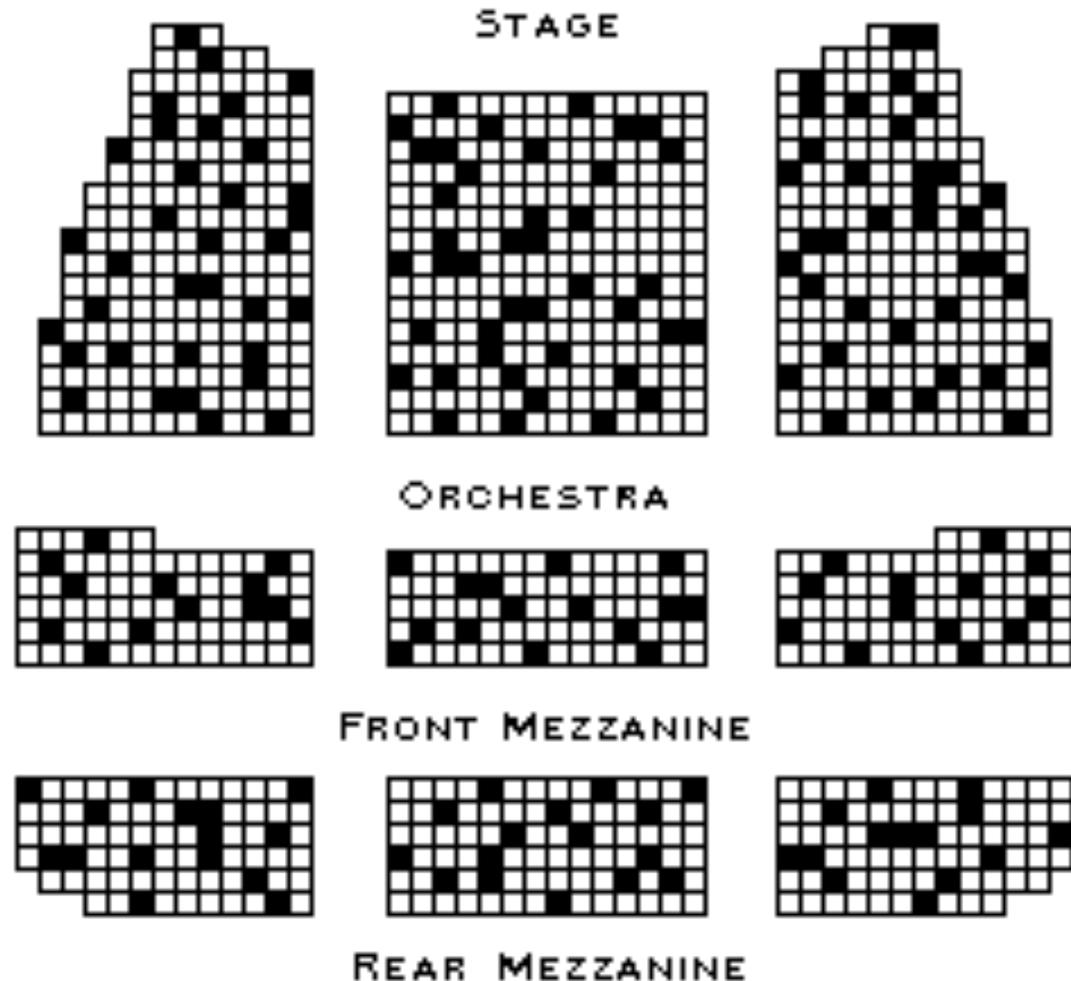
# 1. Smoking

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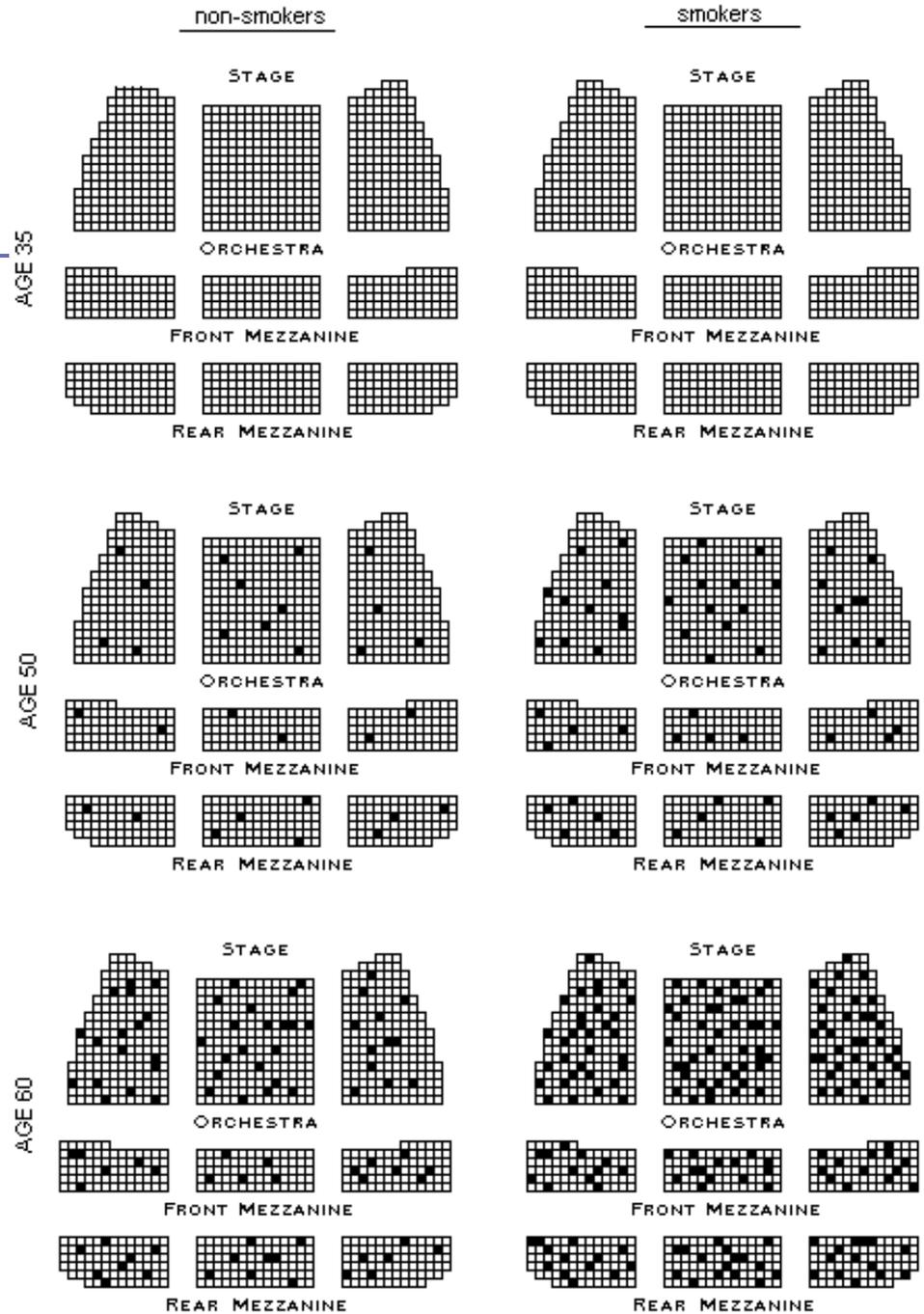
- ❖ We all agree that smoking is harmful, but how harmful is it?
- ❖ Two major studies have tracked populations that smoked and populations of non-smokers
  - Seven Countries Study (observed death rates over 25 years in middle-aged men)
  - British Doctors Study (observed death rates over 50 years in male doctors in the UK)

# Seven Countries Study Smoking RCT

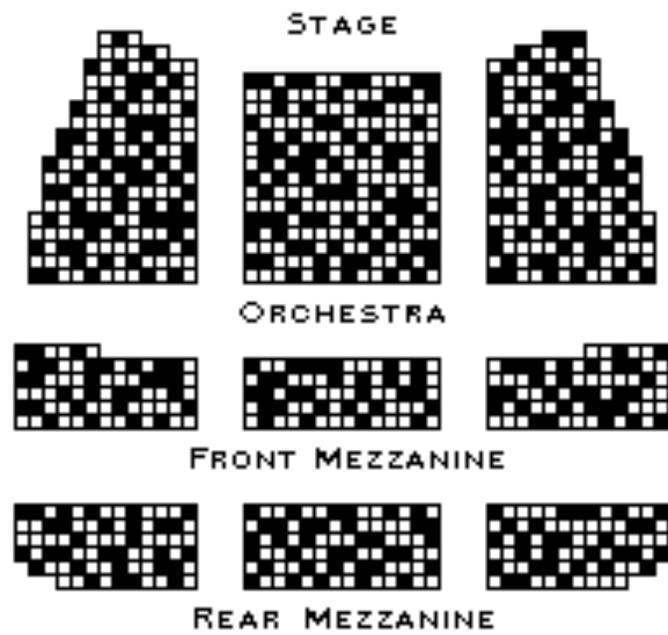
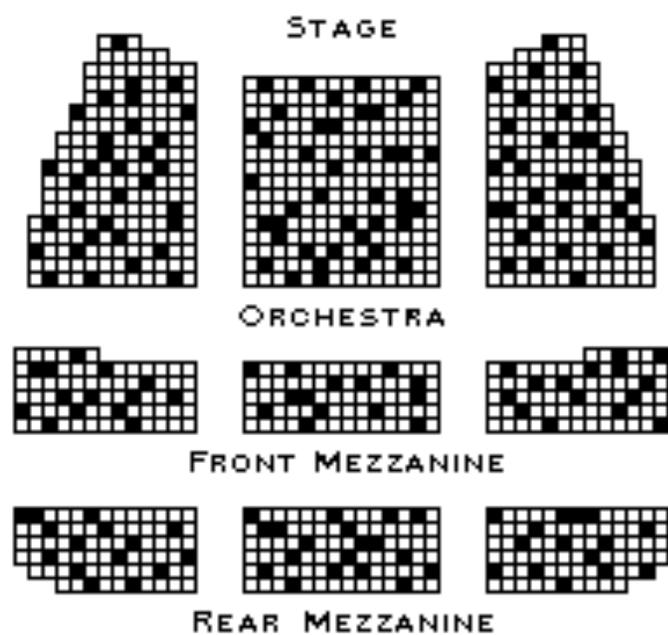
The darkened seats in this theater of male smokers represent the 198 extra deaths observed over 25 years compared to a theater of male non-smokers.



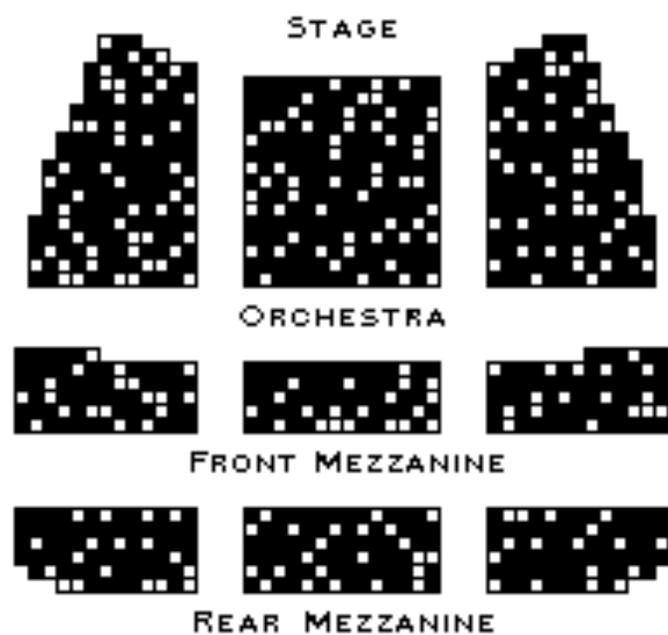
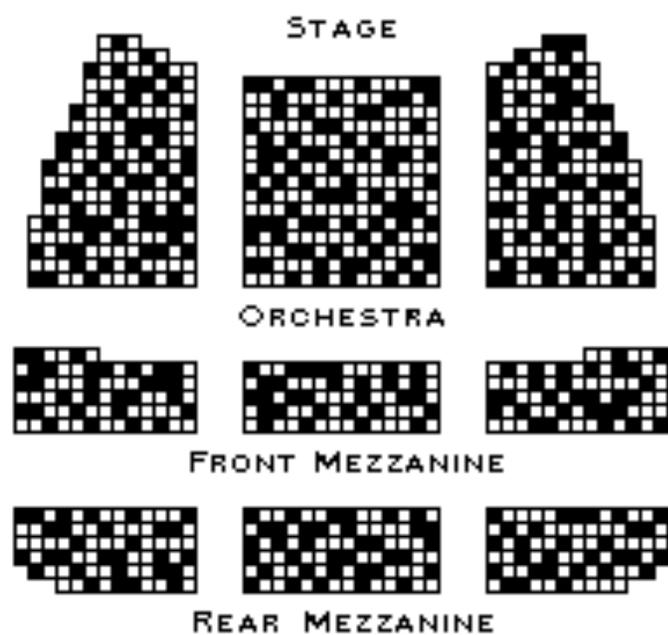
# British Doctors Smoking RCTs



AGE 70



AGE 80



## 2. Drinking Water and Health Risks

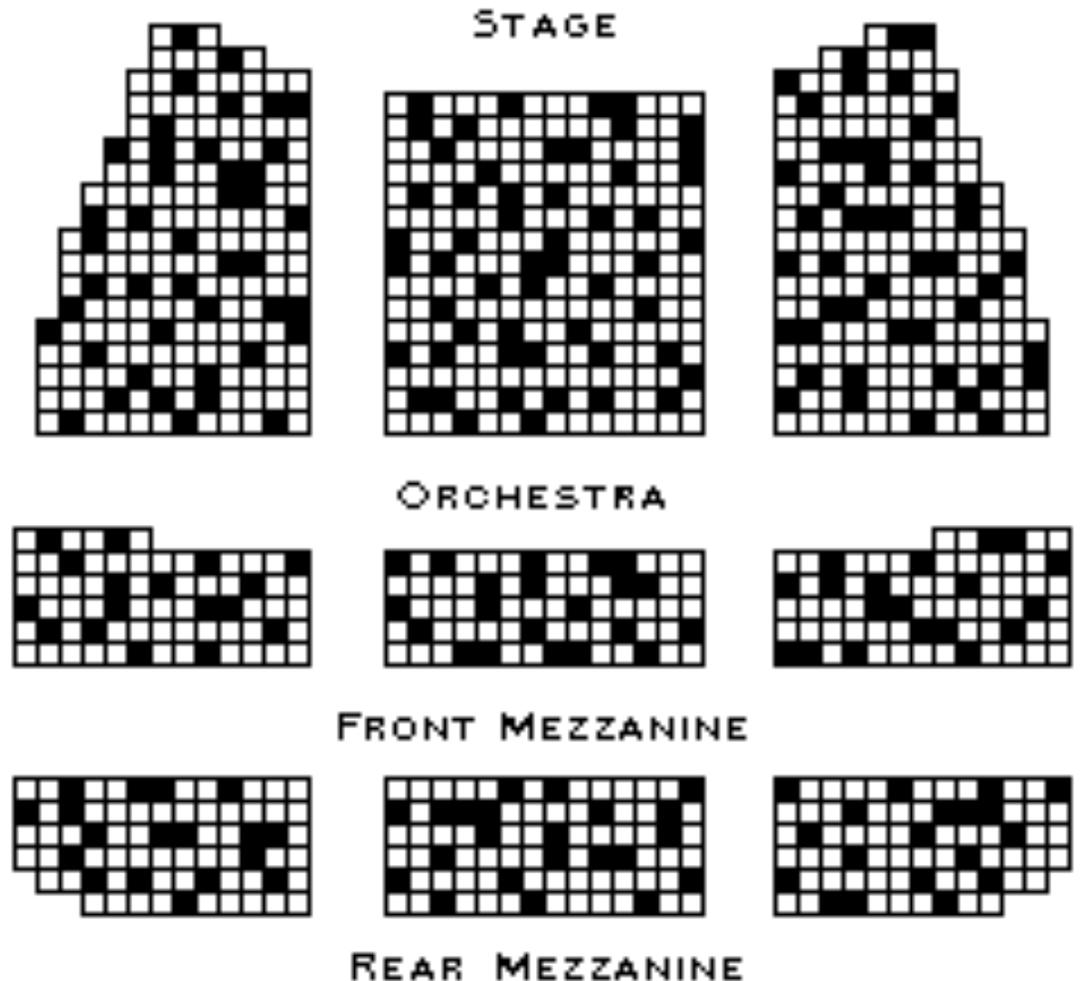
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- ❖ High risk of getting sick from drinking untreated drinking water
- ❖ We safeguard our drinking water using some form of chlorination
- ❖ Chlorine reacts with organic matter in the water, transforming them into carcinogenic disinfection by-products (DBPs)
- ❖ Trade-off between pathogens making us sick and DBPs presenting a cancer risk

# Sickness from Contaminated Drinking Water RCT (daily risk)

Ingestion of 100 *Salmonella* cells

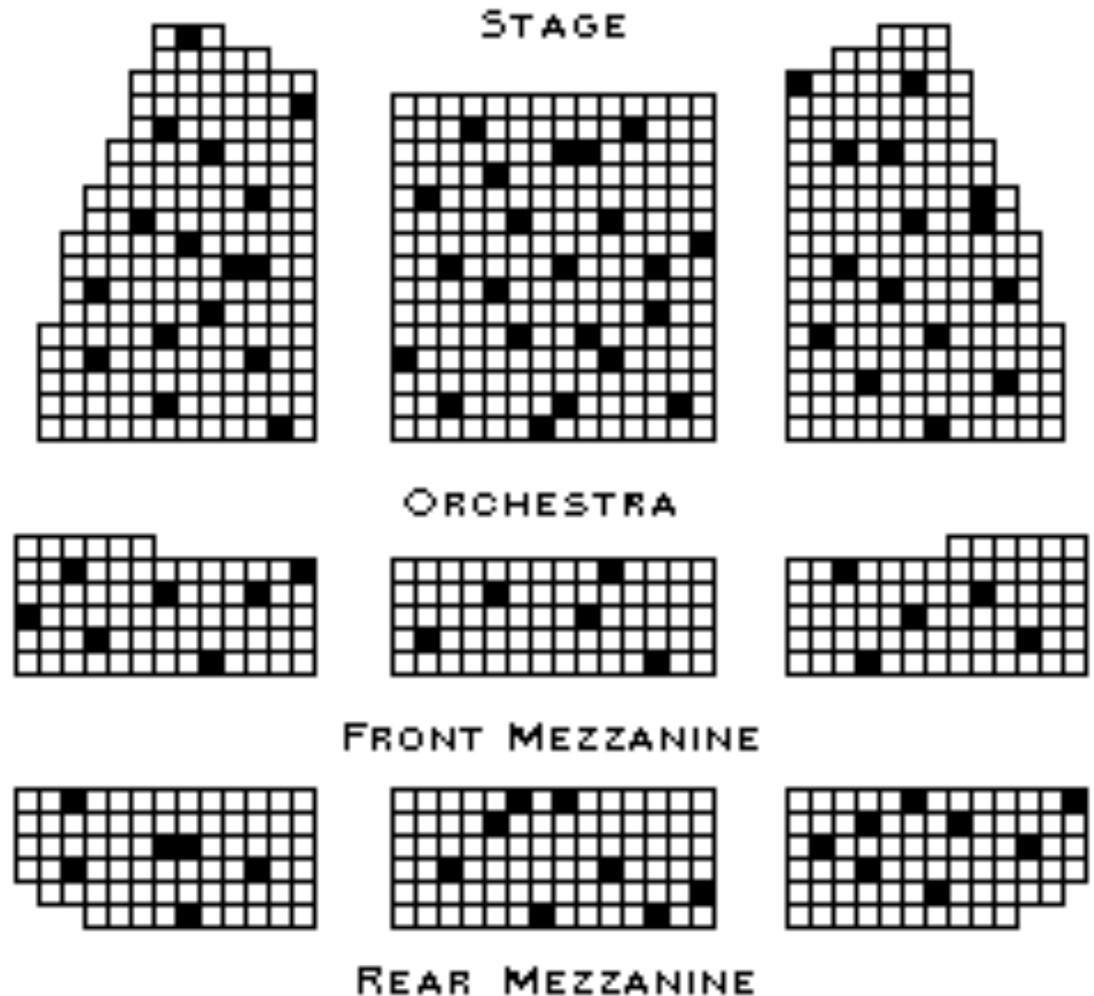
260 individuals out of 1,000 are expected to get sick in one day



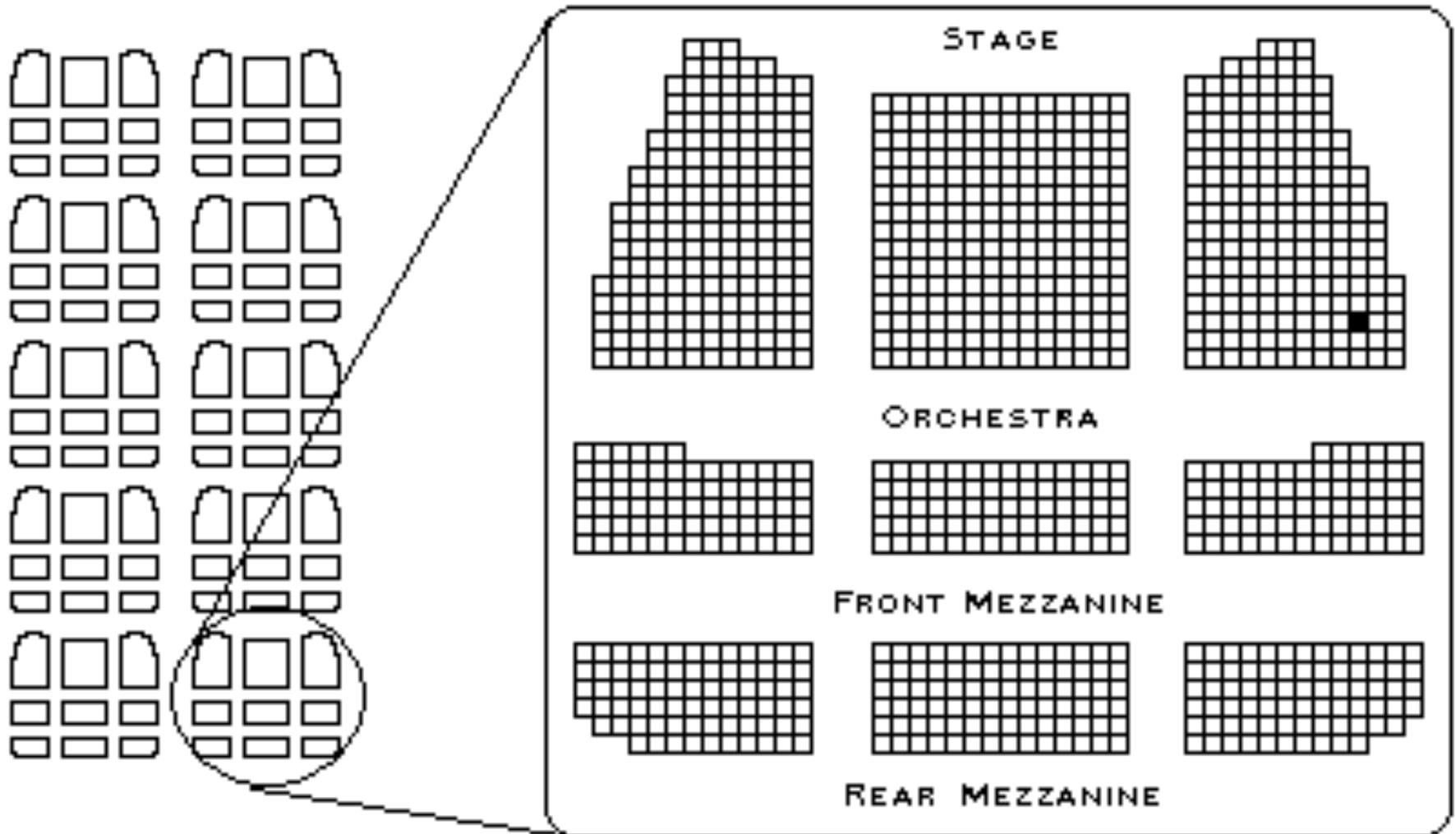
# Death from Contaminated Drinking Water RCT (yearly risk)

Ingestion of 100 *Salmonella* cells a day for one year

92 individuals out of 1,000 are expected to die over the year



# Chlorinated Drinking Water RCT (lifetime risk of cancer with DBPs at MCL)



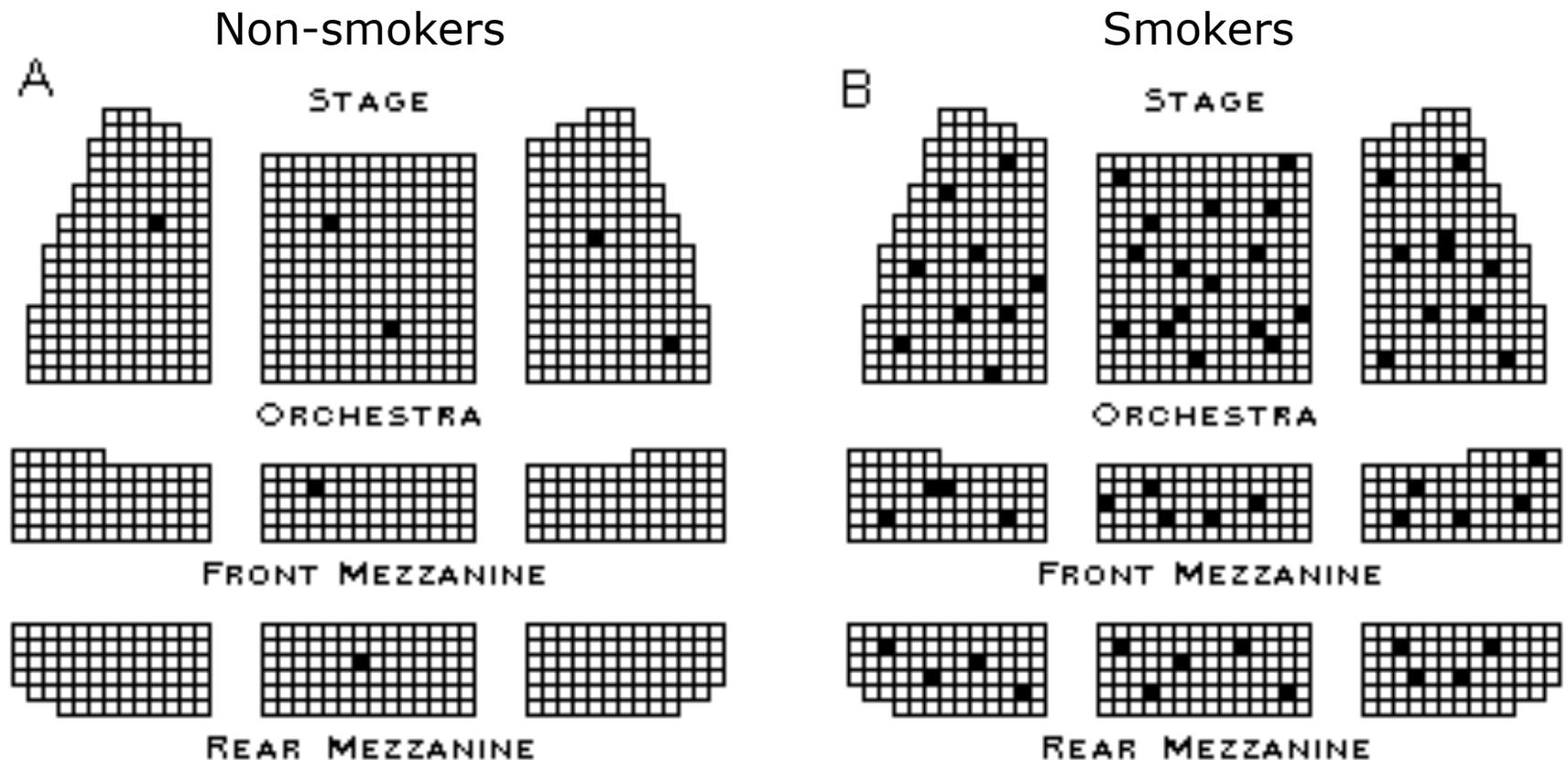
### 3. Exposure to Residential Radon

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- ❖ Radon is a colorless, odorless, radioactive gas formed by radioactive decay of uranium
- ❖ Seeps out of the ground and can accumulate in buildings
- ❖ When radon is inhaled, the alpha radiation can eventually cause lung cancer
- ❖ Lung cancer death rates in underground miners are used to estimate lung cancer risk at the low radon levels we might find in our homes
- ❖ Smoking renders your lungs more vulnerable to radon damage

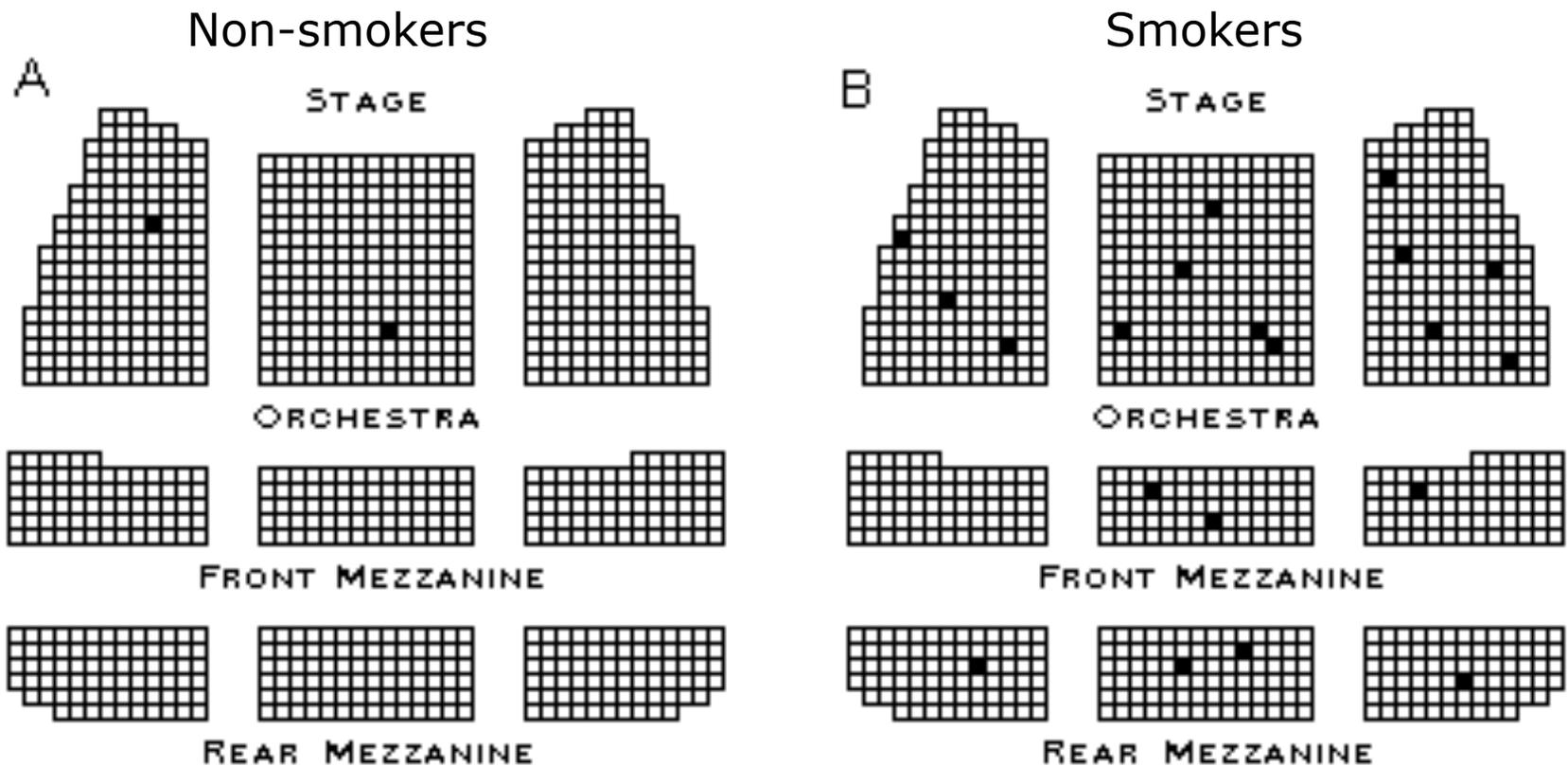
# Radon RCT at 4 pCi/liter

## Regulatory Guideline Set by the EPA



# Radon RCT at 1.3 pCi/liter

## Average Level in US Homes



## 4. Cholesterol and Heart Disease

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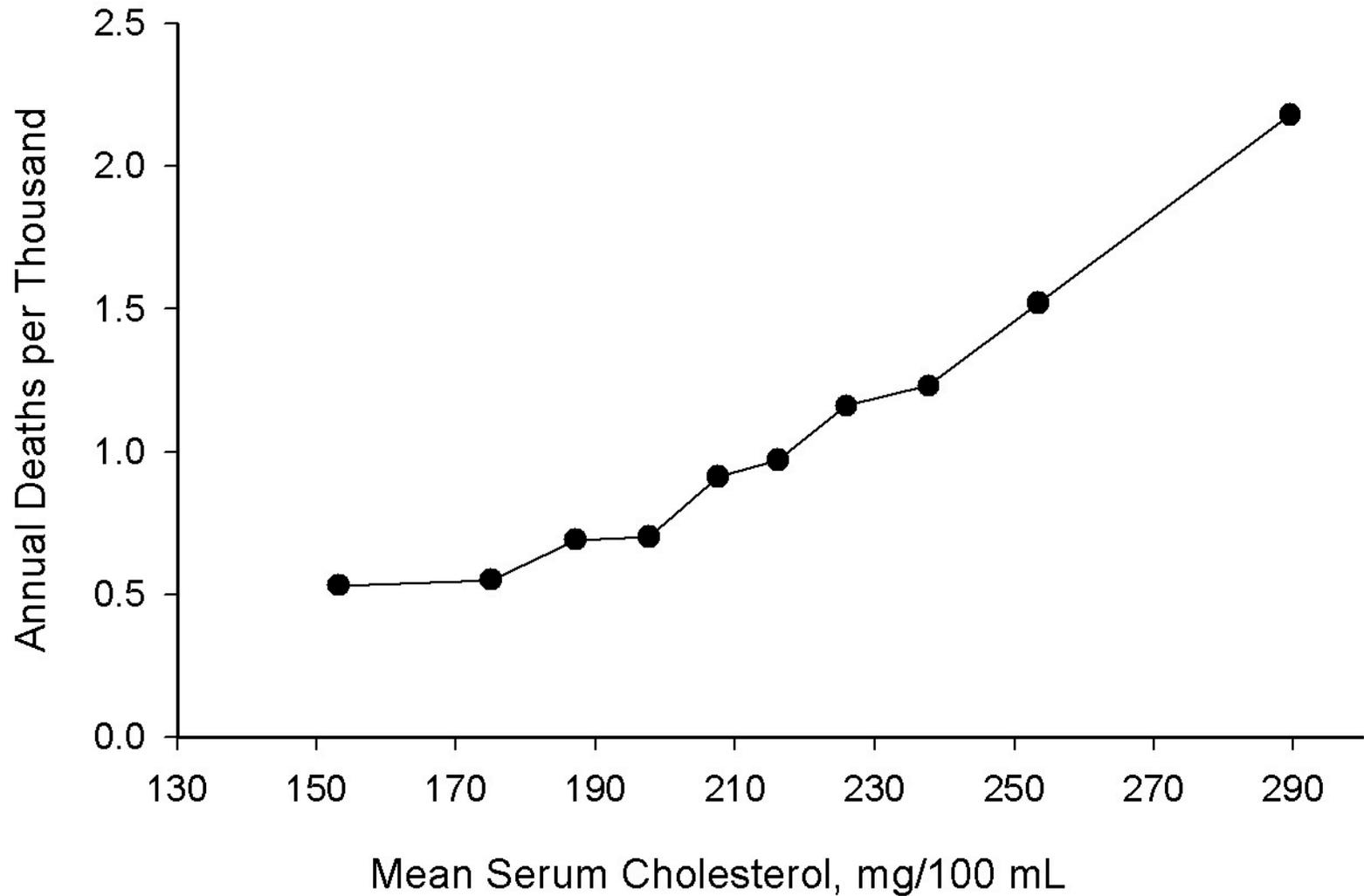
- ❖ Coronary heart disease (CHD) is the leading cause of death in industrialized countries
- ❖ Accounts for 40% of all deaths in the US
- ❖ The causes of CHD and of its precursor, atherosclerosis, are still unknown
- ❖ Prevailing view is that elevated blood serum cholesterol is the primary risk factor for CHD
  - Reports state that CHD risks are markedly lower with low cholesterol (current benchmark of 200 mg/100 mL)
  - Reports state that lowering cholesterol dramatically reduces the risk of suffering from CHD
  - FDA policy: Any treatment that lowers cholesterol levels automatically is considered to decrease the risk of CHD
- ❖ 200 million Americans undergo cholesterol screening tests, 13 million are on cholesterol-lowering drugs, and 52 million are on cholesterol-lowering diets

# What is the Relationship Between Cholesterol and CHD?

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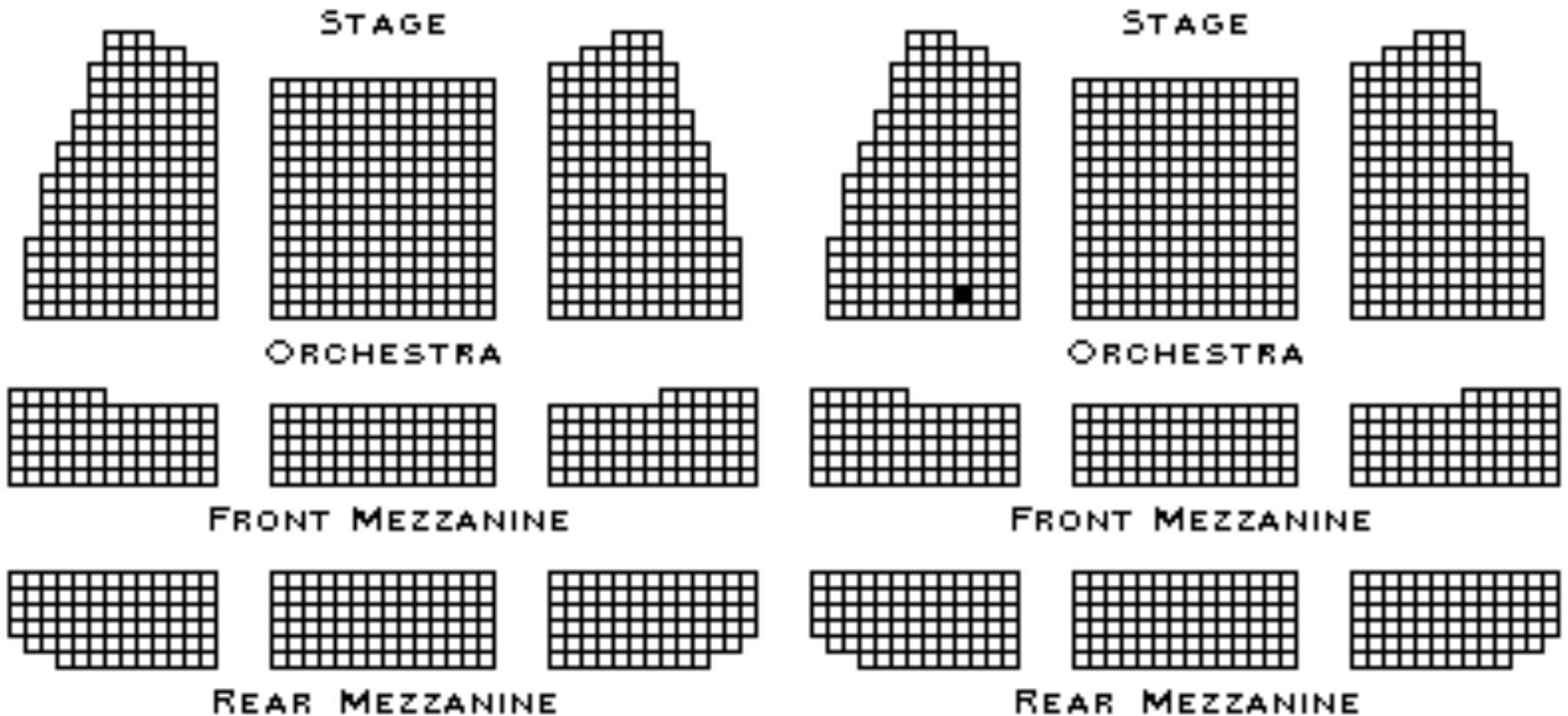
- ❖ Key question: Within a population, do individuals with essentially normal blood serum cholesterol have a lower incidence of CHD than individuals with elevated levels of blood serum cholesterol?
- ❖ Two well-known clinical studies
  - Framingham (5,000 men and women from a Boston suburb were followed for 50 years starting in 1948)
  - MRFIT (350,000 male participants had their cholesterol levels measured and monitored for 6 years in the 1980s)

# Annual CHD Deaths vs. Cholesterol (MRFIT Study)



# Cholesterol RCT

Out of 2,000 people with elevated cholesterol, there will be one additional death each year from CHD as compared to 2,000 people with normal cholesterol



# Implications

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- ❖ This means that 99.95% of the population would not benefit from efforts (diet and/or drugs) to reduce blood serum cholesterol levels.
- ❖ To put it another way, for 1,999 out of 2,000 individuals each year, it makes no difference whether they have elevated cholesterol or normal cholesterol, in terms of whether or not they develop coronary heart disease.
- ❖ Others agree with this assessment
  - Dr. Ridker: Half of all heart attacks and strokes occur in individuals without elevated cholesterol levels
  - Dr. DeBakey: Elevated cholesterol levels had no effect on the recurrence of coronary disease
  - Dr. Kannel: Diagnosis of overt heart disease on the basis of lipid [cholesterol] levels alone is simply not feasible
  - Dr. Ravnskov: People whose blood cholesterol is low develop just as many plaques in their blood vessels as people whose cholesterol is high

# Recent Study with Vytorin

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- ❖ Vytorin is a combination of Zetia and Zocor--the two drugs lower LDL cholesterol by different mechanisms
- ❖ The intent was that the combination would be more effective at lowering cholesterol, which it did
- ❖ Unfortunately, it did not slow the accumulation of fatty plaques in the arteries
- ❖ Several articles have now appeared in the NY Times that raise doubts about the current belief that lowering cholesterol is the key to cardiovascular health
- ❖ The full two page ad from the drug companies to counter the results is striking

## 5. Statins, Cholesterol, and CHD

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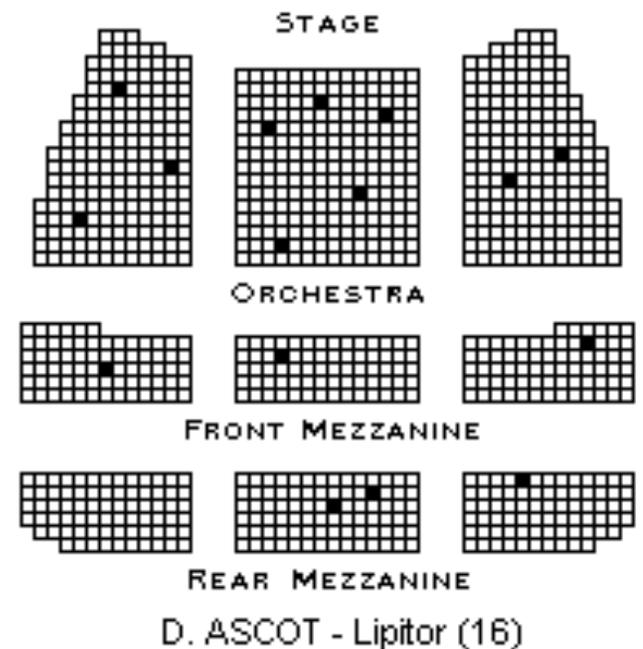
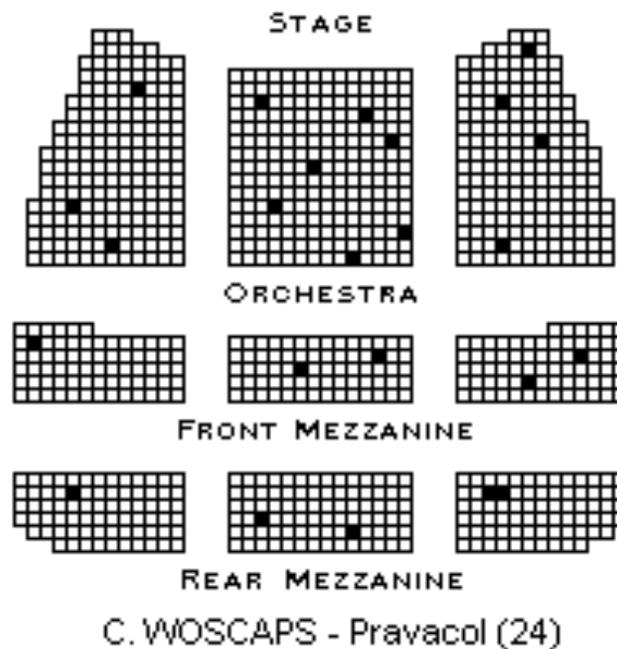
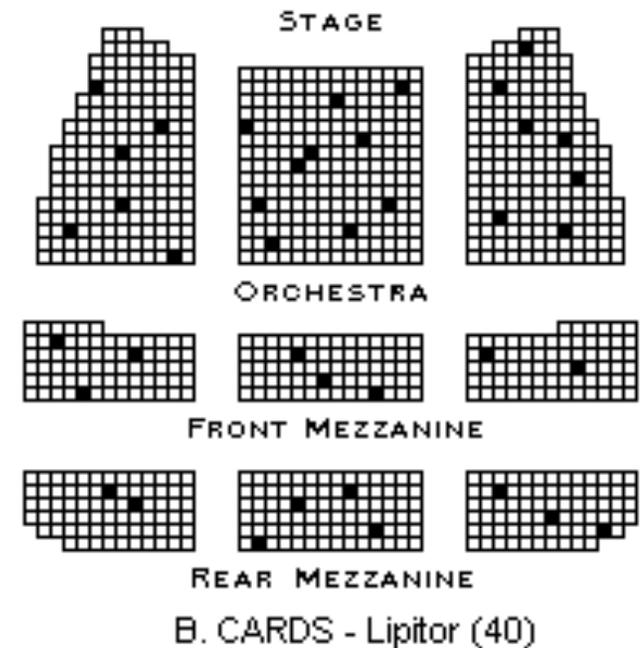
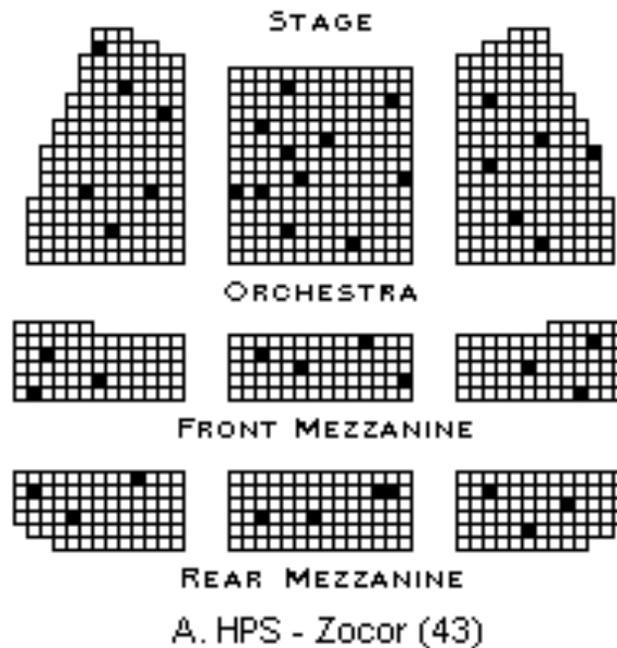
- ❖ Statins--Lescol, Lipitor, Mevacor, Pravacol, and Zocor--are the most widely used prescription drugs in the world
- ❖ Annual sales of \$16 billion in 2001
- ❖ Statins inhibit an enzyme that is used to make cholesterol. Cells then develop more receptors to take up cholesterol from the blood.
- ❖ Statins facilitate many other reactions, such as lessening inflammation of arteries
- ❖ Several clinical trials with statins have been conducted

# Statins

## RCTs--

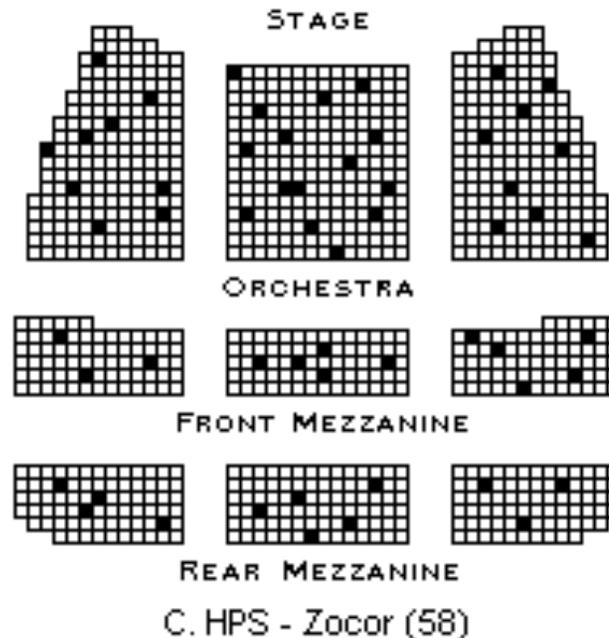
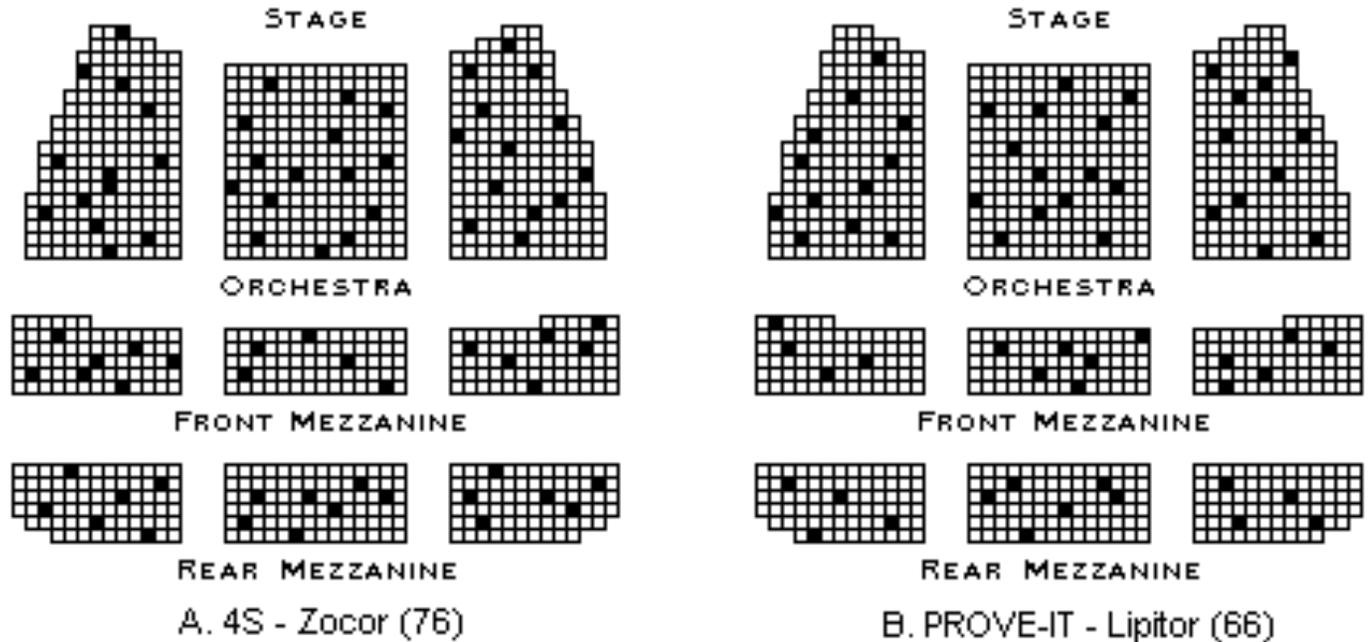
### Primary Prevention

The darkened seats in each RCT represent the number of individuals out of 1,000 who avoided CVD over a 5-year period by taking statins, as compared to people who didn't take statins.



# Statins RCTs-- Secondary Prevention

The darkened seats in each RCT represent the number of individuals out of 1,000 who avoided CVD over a 5-year period by taking statins, as compared to people who didn't take statins.



# Implications

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- ❖ The absolute benefit rate for using the statins for primary prevention is about 3%
- ❖ The absolute benefit rate from using the statins for secondary prevention is almost 7%
- ❖ Statins provide benefits greater than the benefits which would be achieved by lowering blood serum cholesterol levels
  - Mechanisms other than the lowering of cholesterol appear responsible for the reduced incidence of CVD following statin use
- ❖ Cholesterol level appears to be the wrong marker to decide statin use

# Acceptable Health Benefits and Risks

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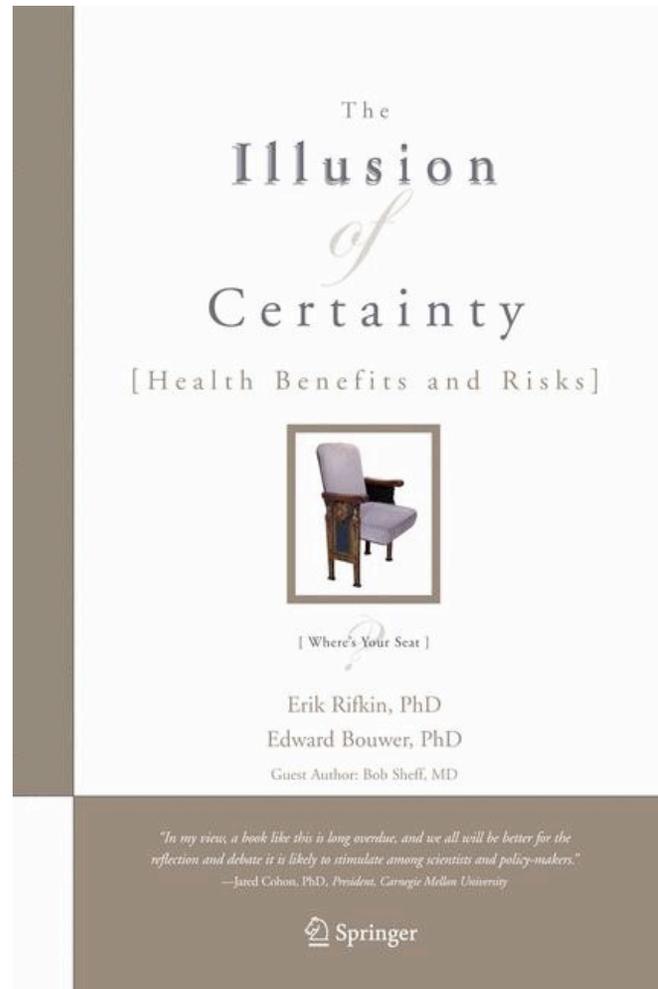
- ❖ Based in large part on public acceptance, political agenda, and economic considerations
- ❖ Science is not involved in the process
  - We accept and reject risks every day
  - An acceptable risk is your own decision or a policy decision
- ❖ EPA has set a target range for carcinogens of 1 in 10,000 to 1 in 1,000,000 for acceptable risks
- ❖ No analog in the medical field
  - There is not an accepted value for the number of individuals who would have to benefit from medical intervention
  - Based on the perspectives and values of the organizations that manage these health issues
  - Easy to have doubts about your doctor's recommendations

# Concluding Remarks

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- ❖ Having the proper data available in a user-friendly format (e.g., RCT) will enable each of us to determine the level of benefits and risks which we can accept
- ❖ We need to present absolute values and move away from relying solely on relative values
- ❖ We are being overtreated
  - It is estimated that we spend between 1/5 and 1/3 of our health care dollars on care that does nothing to improve our health
  - RCTs can aid decisions about eliminating current health care that brings little or no health benefits
- ❖ Debates on the pros and cons of Universal Health Care should also focus on ways to reduce the rate of spending on health care
  - 4.3 trillion dollars a year by 2017

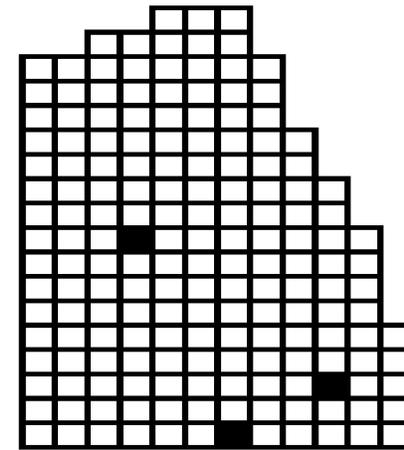
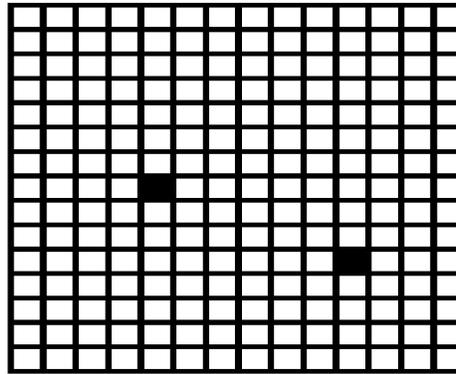
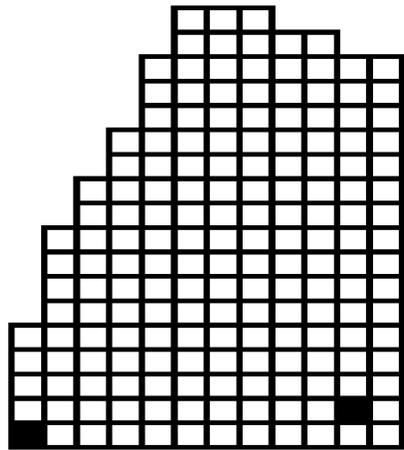
# Questions?



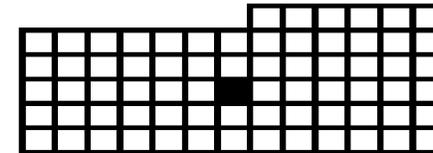
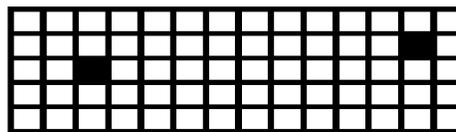
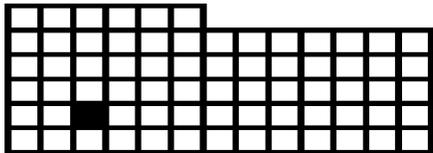
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# Vioxx™ RCT

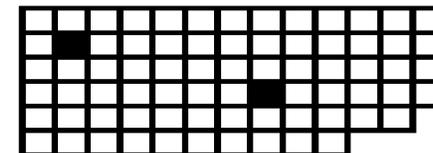
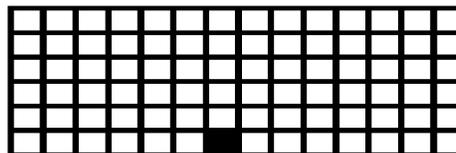
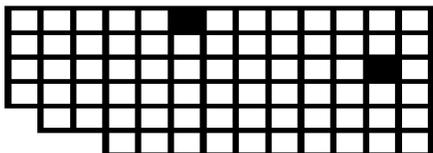
Stage



Orchestra

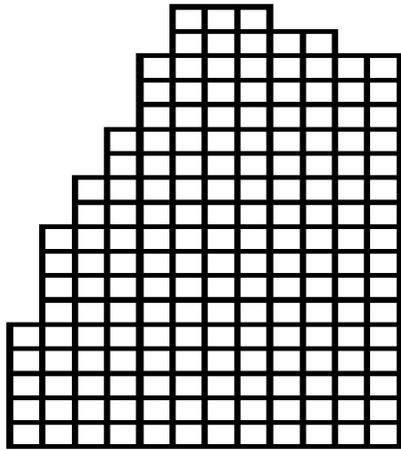


Front Mezzanine

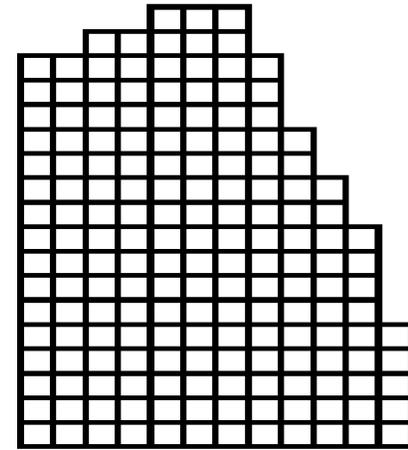
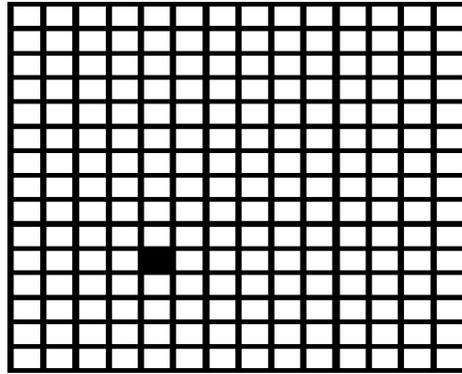


Rear Mezzanine

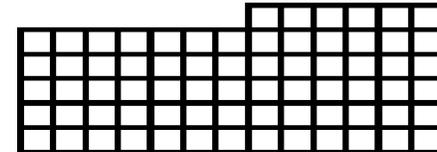
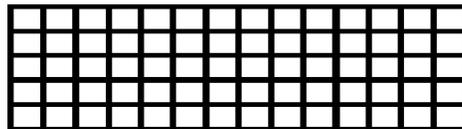
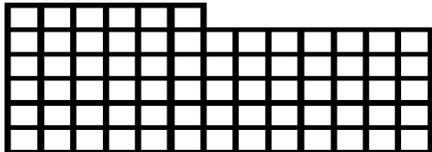
# Mammogram RCT



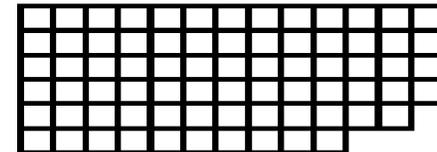
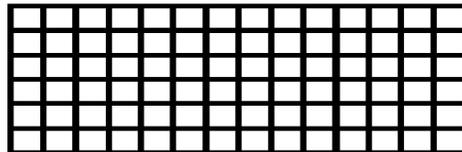
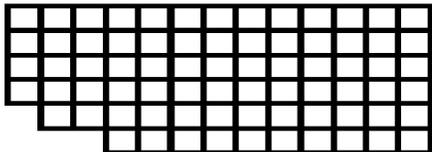
Stage



Orchestra



Front Mezzanine



Rear Mezzanine