

Proceedings of The Institute of Food Technologists' First Annual Food Protection & Defense Research Conference

November 3-4, 2005
Atlanta, Georgia

[Session: **Modeling and Risk Assessment**]

Applying Risk and Decision Analysis to Food and Animal Health and Security

DR. VICKI BIER, DR. LORNA ZACH
UNIV. OF WISCONSIN-MADISON

Many of the other talks at this conference are a good introduction to my presentation today. While Dr. Zach and I do not have a background in animal epidemiology, we are looking at how tools of engineering risk analysis can be applied to human and animal epidemiology, as well as to food safety. In particular, we want to apply these tools to those problems of interest to the Center for Foreign Animal and Zoonotic Disease Defense.

We have only recently started this work, so I won't talk about our results today. Instead, I will focus on examples of the methodology, using some food-safety examples from the published literature. Fundamentally, in risk assessment, we define risk as a function of both the likelihood of something bad happening, and the severity of that outcome (see Slide 2). For example, Kaplan and Garrick (1981), defined risk as involving both uncertainty and some kind of loss or damage. I'm going to focus in this talk on the uncertainty quantification (as shown in light blue on Slide 2), rather than the consequences. Risk assessment provides "A means to characterize and reduce uncertainty to support our ability to deal with catastrophe through risk management" (Zimmerman and Bier 2002; see Slide 3). Fundamentally, risk management is a decision process. It is a social and political process by which people decide what to do, while taking into account a wide variety of factors. Risk assessment is an input to the process, and provides technical information to inform decision making in light of all these other considerations and value judgments.

The Center for Risk and Economic Analysis of Terrorism Events (CREATE), based at the Univ. of Southern California and funded by the Dept. of Homeland Security, has defined a process that includes four basic modeling steps (see Slide 4). The first step is risk assessment, followed by consequence assessment (that is, how bad the outcome could be, once we know the likelihood of something bad happening). The third step refers to what types of emergency response actions are available to help mitigate the consequences. Finally, the economic assessment is done, based on the severity of the final consequences (taking into account the emergency response; this step determines the total economic impact of the event (above and beyond the health or mortality consequences), and so completes the list of input needs that a decision maker might have.

The overall goal of risk assessment is that it be "credible and fully defensible" (American Industrial Health Council and others 1989; see Slide 5). In particular, it should provide a comprehensive statement of the current uncertainties, so that if you have a good risk assessment in hand, there should be a small chance of "after-the-fact surprises."

Therefore, a good risk assessment should have large uncertainty bounds if the true uncertainties are large, rather than focusing on a best estimate and then finding out later that the true situation was much better or worse than the best estimate.

The intent is that a good risk assessment "explicitly and fairly conveys scientific uncertainty, including a discussion of research that might clarify [and reduce] the degree of uncertainty" (American Industrial Health Council and others 1989). Once we know how big the uncertainties are and where they arise in the risk assessment, we can use this knowledge to prioritize decision making about where to spend our research dollars to reduce risk in the long term, as well as which protective measures should be put in place in the short term.

Note that many of the sources of uncertainty that we address in a risk assessment may not be adequately addressed by some of the current models. For example, current epidemiological models may do a good job of predicting what will happen if a particular strain of foot-and-mouth disease is introduced into the U.S. However, when making decisions about which protective measures to put in place, we will not know which strain will be brought into the country. This gives rise to some additional uncertainties, beyond those addressed by most current models. Similarly, we currently do not know the extent to which foot-and-mouth disease can be spread by airborne mechanisms. Of course, we could run an epidemiological model assuming that there is significant airborne spread, and then run it again assuming that there is not, but ideally, it would be nice to be able to integrate these two possibilities and get an overall statement of uncertainty about the outcomes of an outbreak (given our uncertainty about airborne spread).

To further clarify these issues, I'd like to introduce terminology to distinguish between "state-of-knowledge" uncertainty (scientific uncertainty) and "population variability" (Kaplan 1983; see Slide 6). For example, variability might refer to differences from one person to another, or from one animal to another, whereas state-of-knowledge uncertainty represents systematic scientific uncertainty. As an example of state-of-knowledge uncertainty, we would typically not yet know much about the effectiveness of a vaccine that had not yet been fully developed. These factors are also sometimes described as aleatory uncertainty (variability) and epistemic (state-of-knowledge) uncertainty (Paté-Cornell 1996).

You can have uncertainty without variability; for example, if all animals are equally susceptible to a particular disease, but we don't know much about their level of susceptibility. Similarly, you can have variability without uncertainty. For example, if we knew that the risk of some

particular pollutant to children was systematically different than its risk to adults, but did not know the actual risk to either group, then we would have variability by age and also uncertainty. However, if we knew the actual risk levels to both children and adults, then we would not have scientific uncertainty, only variability.

Of course, in most real-world situations, we will have both state-of-knowledge uncertainty and population variability, and they can be difficult to disentangle from each other. In fact, the difference between variability and uncertainty is not necessarily fundamental. For example, some sources of uncertainty might be effectively irreducible in the short term (say, in the next 6 mo), if there is not enough time to research them before a decision must be made. However, if we're also trying to set longer-term research agendas, then a lot of uncertainties that are irreducible in the short term might be researchable through programs that would yield good answers 5 or 10 y from now.

Monte Carlo simulation is commonly used to help predict what might happen in a disease outbreak. Here, I'm going to talk about a variant of that methodology that is called "2-dimensional Monte Carlo analysis" (see Slide 7). The purpose of this approach is to create a single overall statement of uncertainty, including not only the types of randomness and variability that are already commonly taken into account in simulations, but also systematic scientific uncertainties (such as lack of knowledge about infectiousness, susceptibility, and so on). This is important, because randomness and variability have different implications for policy than broader scientific uncertainties. So, while it is nice to have a single overall statement of how uncertain we are, we also want to be able to distinguish variability from scientific uncertainty in order to look at their different policy implications.

To make this more understandable, I will use as an example a simulation of a fast-food franchise (see Slide 8). If I already owned a franchise at a particular location, I may have variability from day to day in how many people come into that store, how long it takes to serve them, and what they order. However, in this case, I would most likely have a lot of data with which to characterize the average arrival rate of customers and their average service time, so I would have variability with little or no uncertainty.

By contrast, if I were planning to open a new franchise that doesn't exist yet, at a different location where there are currently no fast-food restaurants, then I would have not only variability from customer to customer and from day to day, but also uncertainty about how many customers will arrive on average. Capturing this uncertainty in my simulation and looking at its effect on the profitability of my restaurant might help me make decisions. For example, if the analysis reveals that the arrival rate of customers at this location might be so low as to make a restaurant unprofitable, I could choose to do more market research before deciding whether to open a restaurant at this particular location.

My co-author, Dr. Zach, and I are just starting this process for animal-health risk analysis, so we do not yet have results to present. Therefore, I'm going to present an example of 2-dimensional Monte Carlo from the published food-safety literature (Humphreys and others 2001). This analysis examined a naturally-occurring toxin (fumonisin) in corn and corn products, and potential health concerns for the U.S. population (see Slide 9). There is uncertainty about both the quantity of this toxin in corn-based food products, and also uncertainty about how much corn different people in the U.S. consume. Moreover, while the toxicity of fumonisin has been measured in mice and rats, differences between rodents and humans create uncertainty when extrapolating the animal results to humans. Of course, different humans may also have different levels susceptibility to the toxin. Finally, the mechanism of fumonisin toxicity in humans is uncertain, and it is unclear whether it is more similar to the mechanism of toxicity in rats or mice. Given all of these sources of uncertainty and variability, the government needs to decide whether to regulate allowable levels of fumonisin toxins in corn.

For background purposes, fumonisin is a mycotoxin that grows naturally on corn and maize, which are used for both human and animal consumption throughout the world (see Slide 10). The level of fumonisin contamination in corn depends on weather/climate and other factors. For example, droughts and insect damage make corn more susceptible to the fungus that produces this toxin. (The fungus grows on the corn kernels while they are still on the corn plant, and is often not visible). The severity and effects of fumonisin toxicity vary from species to species with horses being especially sensitive (see Slide 11). In mice, the most sensitive toxicity endpoint is liver cancer, whereas for rats, the most sensitive endpoint is renal lesions. Human data is of course, limited, although it appears that fumonisin could cause a variety of diseases in humans, including esophageal cancer, gastrointestinal diseases, and liver or renal cancers.

In support of policy decisions, the analysis carried out by Humphreys and others (2001) estimated the exposure of the U.S. population to fumonisin, as well as the extent of uncertainty about that exposure (see Slide 12). This uncertainty was treated as the "outer loop" in a 2-dimensional Monte Carlo analysis. By contrast, the variability analysis (or "inner loop") of a 2-dimensional Monte Carlo analysis is simply an ordinary ("one-dimensional") Monte Carlo simulation. In the problem being described here, there is uncertainty about both consumption levels and the amount of fumonisin in corn. The combination of these could result in up to 3 orders of magnitude uncertainty about individual dietary exposure to fumonisin. [Strictly speaking, differences in corn-consumption levels and the extent of fumonisin contamination probably represent variability—from person to person (for consumption levels), and over time (for contamination levels)—rather than uncertainty. However, for consistency, we are adopting the same categorization of uncertainty and variability as used by Humphreys and others (2001).]

The chart on Slide 13 shows the levels of fumonisin that have been measured in different types of corn products in the U.S. (Humphreys and others 2001). For example, corn meal has relatively high levels of fumonisin contamination, while popcorn, corn chips, and corn flakes have much lower levels. For comparison purposes, Canada has had essentially no fumonisin contamination in some years, but higher levels in other years, possibly due to drought conditions (Kuiper-Goodman and others 1996). South Africa often has high levels of fumonisin contamination in corn, possibly due to differences in climate and agricultural practices (Marasas 1997).

Humphreys and others (2001) looked at the effects of various possible regulatory measures on levels of fumonisin consumption. For example, Slide 14 shows fumonisin exposure per person per day as a function of both the level of corn consumption and the maximum allowable concentration of fumonisin in corn. The light blue line at the top of this figure shows the toxin consumption under circumstances with no regulatory limit on fumonisin contamination. As the limit of allowable fumonisin contamination in corn is reduced (down to 0.5 parts per million), the exposure to the toxin decreases (as we would expect).

However, interestingly, reducing the allowable contamination level may not substantially reduce the exposure levels of vulnerable individuals with the greatest corn consumption. This suggests that those individuals with high levels of corn consumption may still be heavily exposed to fumonisin, even if the corn itself is less heavily contaminated.

Humphreys and others (2001) also studied the effects of consumption advisories (see Slide 15). Under this alternative, government authorities could advise people to limit their intake of certain corn products, in a similar manner to what is now done for Great Lakes fish. The chart on Slide 15 is similar to the previous one, but shows the effects of differing consumption advisories on total fumonisin intake, as a function of people's (original) levels of corn consumption. The light blue line at the top again shows the extent of fumonisin intake with no

consumption advisory. As the recommended consumption limit in advisory decreases, the daily toxin intake is markedly reduced. Thus, consumption advisories would seem to have a greater effect on reducing peak levels of fumonisin intake than contamination limits, because consumption advisories specifically address risks to those individuals who consume large amounts of corn.

Humphreys and others (2001) also studied the effects of variability, or the “inner loop” of the Monte Carlo simulation (see Slide 16). In their study, the variability was taken to include the effects of extrapolation from rats to humans, differences between individuals (for example, due to different body weights), and the inadequacy of the data available for characterizing the dose-response relationship to fumonisin. [Again, the effects of extrapolation from rats to humans and the inadequacy of dose-response data would perhaps be better characterized as contributing to uncertainty rather than variability, but for consistency, we are adopting the same terminology as Humphreys and others (2001).] Estimation of the toxicity in Humphreys and others (2001) was based on expert opinion (see Slide 17). Specifically, a pathologist provided ratings of the severity of clinical consequences resulting from different levels of toxin exposure, based on available toxicity information. Ratings ranged from 0 to 3, with 1 representing the smallest observable effect, values less than 1 representing sub-clinical effects, and values close to 3 representing severe effects.

Slide 18 shows the contributions of both uncertainty and variability, as defined by Humphreys and others (2001), to human nephrotoxic risk under a variety of regulatory scenarios. (The graph is dimensionless, because the units can be difficult to interpret.) In Slide 18, the red bars represent the effects of uncertainty with no variability; the purple bars represent variability with no uncertainty; and the cream-colored bars represent the effects of both uncertainty and variability. Thus, for example, the red bars show the estimated risk levels if both corn consumption and the extent of fumonisin contamination (treated as aspects of “uncertainty” in this study) were at relatively high levels. Conversely, neglecting the uncertainty (or “outer loop” of the Monte Carlo simulation) and setting only those factors treated as variability to high levels would give us the purple estimates of risk (rather than the cream-colored estimates). This could result in estimates of risk that are low by about a factor of ten.

Thus, the results on Slide 18 demonstrate the value of 2-dimensional Monte Carlo analysis. In particular, it may sometimes be worthwhile to conduct additional research to reduce uncertainty. In this particular case, those factors categorized as “variability” appear to contribute more to the overall risk than those categorized as “uncertainty,” and in any case, all of the risk estimates were low enough that no further regulatory action was judged to be necessary (see Slide 19). However, in cases where the overall risk estimates are higher, it could be important to take uncertainty into account in order to avoid underestimating peak risks. Some of the risk-management options that could have been considered if fumonisin risks had been too high might include contamination limits and consumption advisories (see Slide 20). Limits on the maximum toxin levels in corn products put the burden of risk reduction on corn producers. By contrast, consumption advisories (which seem to be more effective at controlling peak exposures) put the burden on consumers.

If consumption advisories were to be adopted, it would be desirable to collect information on vulnerable population subgroups (such as the young, the poor, and pregnant women), as well as data on consumption levels by ethnicity and region. By contrast, if any regulatory efforts were to take the form of contamination limits, then additional information on toxin concentrations by region might be useful, along with information on how contaminated corn might move through the supply chain.

To summarize our discussion of Humphreys and others (2001), I want to emphasize that the conclusion of this study showed only low

levels of risk, and little reason for concern about fumonisin levels in the U.S. corn supply (see Slide 21). However, there are some caveats to that conclusion. In particular, risks may not be as low as indicated above if the data on corn consumption are not representative of the entire U.S. (for example, if some high-consumption regions were omitted), and if the measured levels of fumonisin in corn crops did not include data obtained under drought conditions. Finally, Humphreys and others (2001) assumed that kidney lesions are the most sensitive toxicity endpoint in humans. If some other endpoint is more important than kidney lesions, then the risk could again be higher than indicated here.

As documented in Slides 22 and 23, much higher levels of fumonisin contamination in corn products have been observed in South Africa (Marasas 1997). Moreover, the risks of fumonisin toxicity are especially high for poor populations that subsist on corn as a dietary staple, and that may not be able to afford to buy clean, uncontaminated corn (Marasas and others 1988). The exposures to such populations could well be high enough in some situations to pose a serious hazard.

In the work that Dr. Zach and I are doing for the Center for Foreign Animal and Zoonotic Disease Defense, we hope to be able to apply this technique to control of foot-and-mouth disease (see Slide 24). In particular, this analysis will address not only the effects variability and randomness (for example, due to differences in weather conditions and disease-transmission contacts from day to day), but also some of the scientific uncertainties (such as the infectivity of foot-and-mouth disease). Ideally, we would hope to be able to capture both variability and uncertainty, since they have different implications for decision making. For instance, if different herds have different susceptibility based on their genetics, that problem can't necessarily be solved by further research. Those herds are always going to be different, no matter how much one studies them. By contrast, if there is scientific uncertainty about a factor such as infectivity or airborne spread, that can be addressed by research.

This type of uncertainty analysis can be done for almost any parameter. For instance, some traditional epidemiological models treat parameters such as infectivity (or the differences in infectivity between species) as known constants. With 2-dimensional Monte Carlo simulation, such parameters would not need to be represented by a single number, but could be modeled by a distribution showing the entire range of credible parameter values. In a way, the basic idea is similar to sensitivity analysis. However, instead of having to do a new set of sensitivity runs for each parameter individually, by doing it in an integrated manner, one can study the combined effects of numerous different uncertainties all at once.

One caveat to this type of analysis is that two-dimensional Monte Carlo simulation works well only for uncertainty about the parameters of an individual model. However, in some cases, we may also be uncertain about which model is most appropriate if different models give quite different results (see Slide 25). As noted on Slide 26, Box (1979), an eminent statistician, pointed out that “All models are wrong, but some are useful.” If we know that our model might be wrong and that some other model would give a different result, what can we do about it?

A study by Linkov and Burmistrov (2003) specifically investigated model uncertainty in the context of radioactive contamination on fruit (such as strawberries) in the aftermath of a nuclear power plant accident. The authors found radically different predictions for the cesium concentrations in strawberries from different models. In fact, the results from the 6 different models they considered varied by as much as seven orders of magnitude (see Slide 27).

The graph on Slide 28 shows the ratio of the individual model results to the median output of all 6 models for 4 different iterations of modeling effort. Here, the iterations represent meetings in which the modelers discussed and agreed on their assumptions, and attempted to standardize their modeling methods to achieve greater consistency. As

shown in Slide 28, it was not until the 3rd meeting that major disagreements among the results of the various models were substantially reduced. By iterations 3 and 4, there was much closer agreement among most of the models, but one model still gave much lower predictions than the other 5. Thus, even extensive interactions among the modelers didn't completely eliminate model-to-model difference, suggesting that model uncertainty can be a significant consideration.

What do we do once we have these uncertainty analyses? The first step is to communicate the results to decision makers (see Slide 29). That might be done by using probability distributions to show the overall uncertainty about the outcome of the analysis. For example, probability distributions for the number of infected animals in an outbreak of foot-and-mouth disease might be useful to decision makers in understanding the range of possible scenarios that could occur. Pie charts could also assist in risk communication by showing which sources of uncertainty are contributing the most to the overall uncertainty about the outcome. This kind of information can shed light on the value of additional information, thereby helping in decisions about which uncertainties are the most important to study and resolve. Eventually, the results of the risk assessments can be used as input for a decision analysis, in which stakeholder values are used as a basis for identifying the most desirable risk-management options (see Slide 30).

To conclude, I would emphasize that methods such as two-dimensional Monte Carlo analysis and other forms of uncertainty analysis can be a useful adjunct to more traditional Monte Carlo simulation in supporting decision making (see Slide 31). In particular, uncertainty

analysis can help guide which areas are the most important focus for future research and data collection

References

- American Industrial Health Council, U.S. Environmental Protection Agency, Dept. of Health and Human Services, and Society for Risk Analysis. 1989. Presentation of Risk Assessments of Carcinogens: Report of an Ad Hoc Study Group on Risk Assessment Presentation. Washington, D.C.: American Industrial Health Council.
- Box GE. 1979. Robustness in the strategy of scientific model building. In: Launer R, Wilkinson G, Editors. Robustness in Statistics. New York: Academic Press. p. 201-36.
- Humphreys SH; Carrington C; and Bolger M. 2001. A quantitative risk assessment for Fumonisin B1 and B2 in US corn. Food Add Contam 18(3):211-20.
- Kaplan S. 1983. On a 'two-stage' Bayesian procedure for determining failure rates from experimental data. IEEE Transactions on Power Apparatus and Systems PAS-102:195-202.
- Kuiper-Goodman T, Scott PM, McEwen NP, Lombaert GA, Ng W. 1996. Approaches to the risk assessment of fumonisins in corn-based foods in Canada. In Jackson LS, Devries JS, Bullerman LB, Editors. Fumonisin in Food New York: Plenum Press. p. 369-93.
- Linkov I and Burmistrov D. 2003. Model uncertainty and choices made by modelers: Lessons learned from the International Atomic Energy Agency model intercomparisons. Risk Analysis 23(6):1297-308.
- Marasas MFO. 1997. Risk assessment of fumonisins produced by *Fusarium moniliforme* in corn. Proceedings of the 5th European Fusarium Seminar; Szeged, Hungary. Cereal Res Comm 25:399-406.
- Marasas MFO, Jaskiewicz K, Venter FS, Van Schalkwyk DJ. 1988. *Fusarium moniliforme* contamination of maize in oesophageal cancer areas in Transkei. South Afr Med J 74:110-4.
- Paté-Cornell ME. 1996. Uncertainties in risk analysis: six levels of treatment. Reliability Eng Sys Safety 54:95-111.
- Zimmerman R and Bier VM. 2002. Risk Assessment of Extreme Events. Columbia-Wharton/Penn Roundtable on Risk Management Strategies in an Uncertain World. Palisades, New York; April 12-13. Available from: http://www.ldeo.columbia.edu/CHRR/Roundtable/Zimmerman_WP.pdf.

Applying Risk and Decision Analysis to Food and Animal Health and Security

FAZD CENTER

NATIONAL CENTER FOR FOREIGN ANIMAL
AND ZOONOTIC DISEASE DEFENSE



National Center for Foreign Animal and Zoonotic
Disease Defense

Vicki Bier
Lorna Zach





Risk Assessment

- **Risk depends on both:**
 - Probability or frequency of an adverse outcome
 - Severity of that outcome
- **Kaplan and Garrick (1981) define “risk” as involving “both **uncertainty** and some kind of loss or damage”**

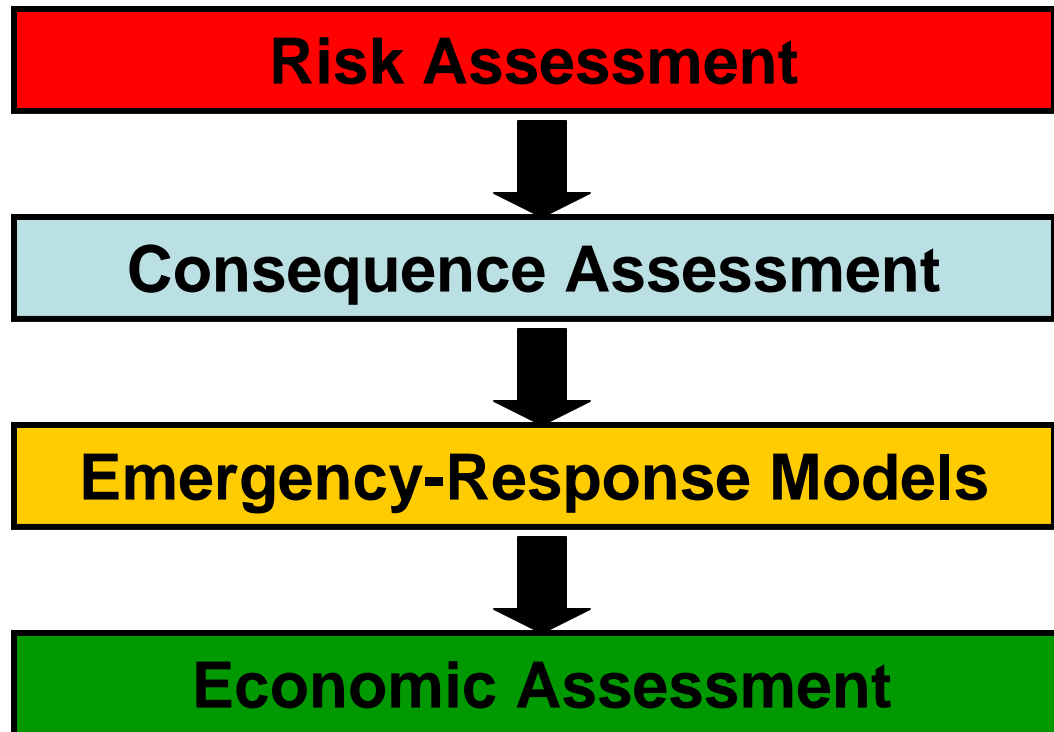


Risk Assessment

- **Risk assessment:**
 - “A means to characterize and reduce uncertainty to support our ability to deal with catastrophe through risk management”
- **Risk management:**
 - Decision-making process
 - Involves political, social, economic, and technical factors



Modeling Steps



(Center for Risk and Economic Analysis of Terrorism Events)



Overall Goal

- **American Industrial Health Council (1989):**
 - Risk assessment should be “credible and fully defensible (so it will not result in after-the-fact surprises)”
 - A good and complete risk assessment “explicitly and fairly conveys scientific uncertainty, including a discussion of research that might clarify [and reduce] the degree of uncertainty”
- **Helps decision makers to quantitatively address sources of uncertainty:**
 - **Many of which are not yet adequately handled by current models**
- **Example:**
 - Uncertainty about airborne spread of foot-and-mouth disease
- **If simulations are run under the assumption that airborne spread can occur (or cannot occur), the results would understate the overall level of uncertainty**



Risk Assessment Terminology

- **Kaplan (1983) distinguishes between “state-of-knowledge” uncertainty and “population variability”**
- **To illustrate, in the context of food risk:**
 - State-of-knowledge uncertainty may refer to a lack of knowledge about the average effect of a particular toxin on health
 - Variability might refer to differences from one person to another
- **One can have uncertainty without variability:**
 - If all exposures result in the same (unknown) risk level
- **and variability without uncertainty:**
 - If the risks to different groups of people are known but unequal



Two-Dimensional Monte Carlo

Create a single overall statement of uncertainty

- **Integrate random effects (e.g., weather conditions) and population variability (e.g., exposure to a disease) with systematic uncertainty (e.g., infectiousness)**
- **Distinguish randomness and population variability from lack of knowledge:**
 - And draw out their different implications for policy

Example



- **Simulations of queuing systems (e.g., in fast-food industry) typically treat the exact number of customers and their service times as random:**
 - Ignore uncertainties about arrival rates and average service times!
- **Two-dimensional Monte Carlo recognizes the uncertainty about the inputs to the simulation**
- **Research and data collection can reduce the uncertainty about arrival rates and average service times:**
 - Even though actual customer arrivals and service times will still be random and unpredictable



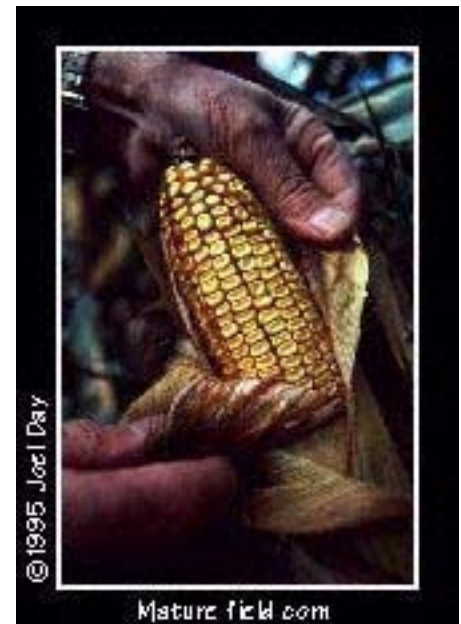
Natural Toxin in Food Supply

- Humphreys, Carrington, and Bolger (2001):
 - “A quantitative risk assessment for Fumonisin B₁ and B₂ in US corn” in *Food Additives & Contaminants* 18(3)
- Complex risk analysis:
 - Uncertain distribution of occurrence in food
 - Uncertain distribution of occurrence in people’s diets
 - Variable attenuation factor between rats and humans
 - Variable response of human population to toxin
 - Uncertain mechanism for NOAEL toxicity
- Should government regulate?
 - Need to assess costs and benefits of regulation



Fumonisin in Corn

- Fumonisin are a group of mycotoxins produced by *Fusarium moniliforme*
- They contaminate corn (maize) used for human and animal feed in all areas of the world
- Level of contamination depends greatly on climate and other factors:
 - Droughts and insect damage can increase contamination
- The fungus producing fumonisin grows on the corn while it is on the plant:
 - And is often not visible





Toxicity of Fumonisin

- Severity and effects vary with species:
 - Horses are the most sensitive to this toxin!
- Most sensitive endpoint in mice is liver cancer lesions:
 - For rats, it is renal lesions
- Human data is limited:
 - May cause esophageal cancer, gastrointestinal diseases, liver or renal cancers





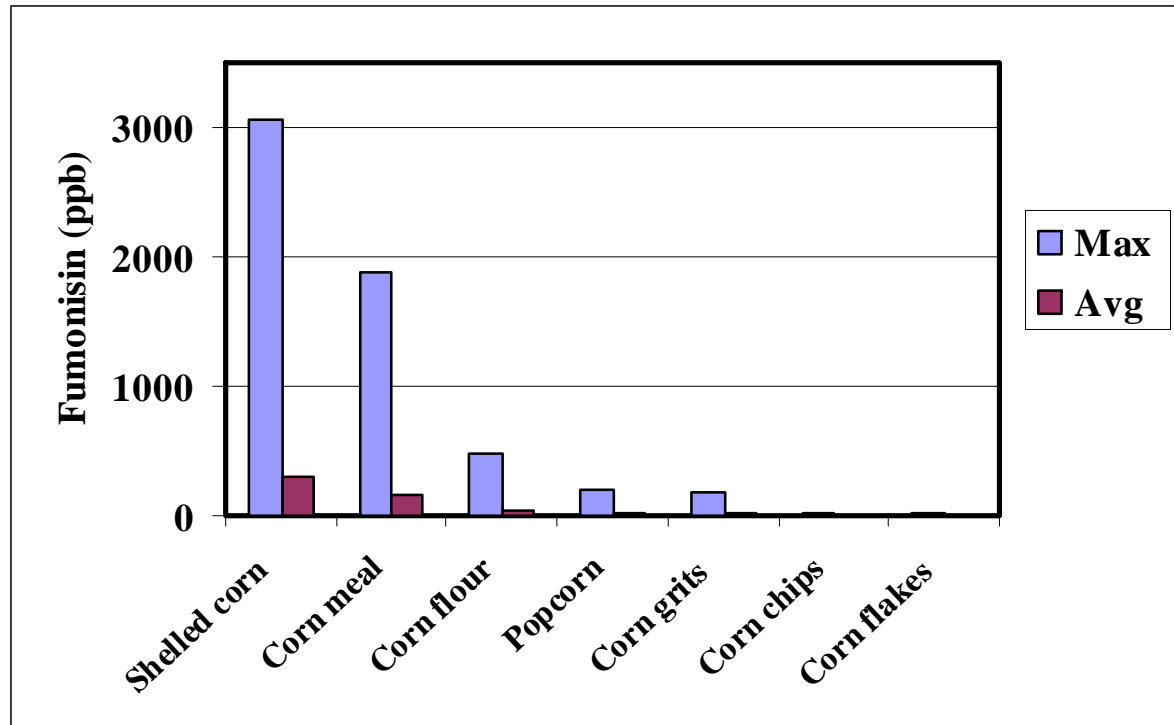
Exposure Assessment

- Estimate US population exposure (and uncertainty about this exposure) to assist in policy analysis:
 - This is the outer (uncertainty) loop in the Monte Carlo
 - Could collect more information to reduce this uncertainty
- There is uncertainty about both:
 - Corn consumption levels
 - Presence of fumonisin in corn products
- Large uncertainty (three orders of magnitude):
 - Range of 1,000!



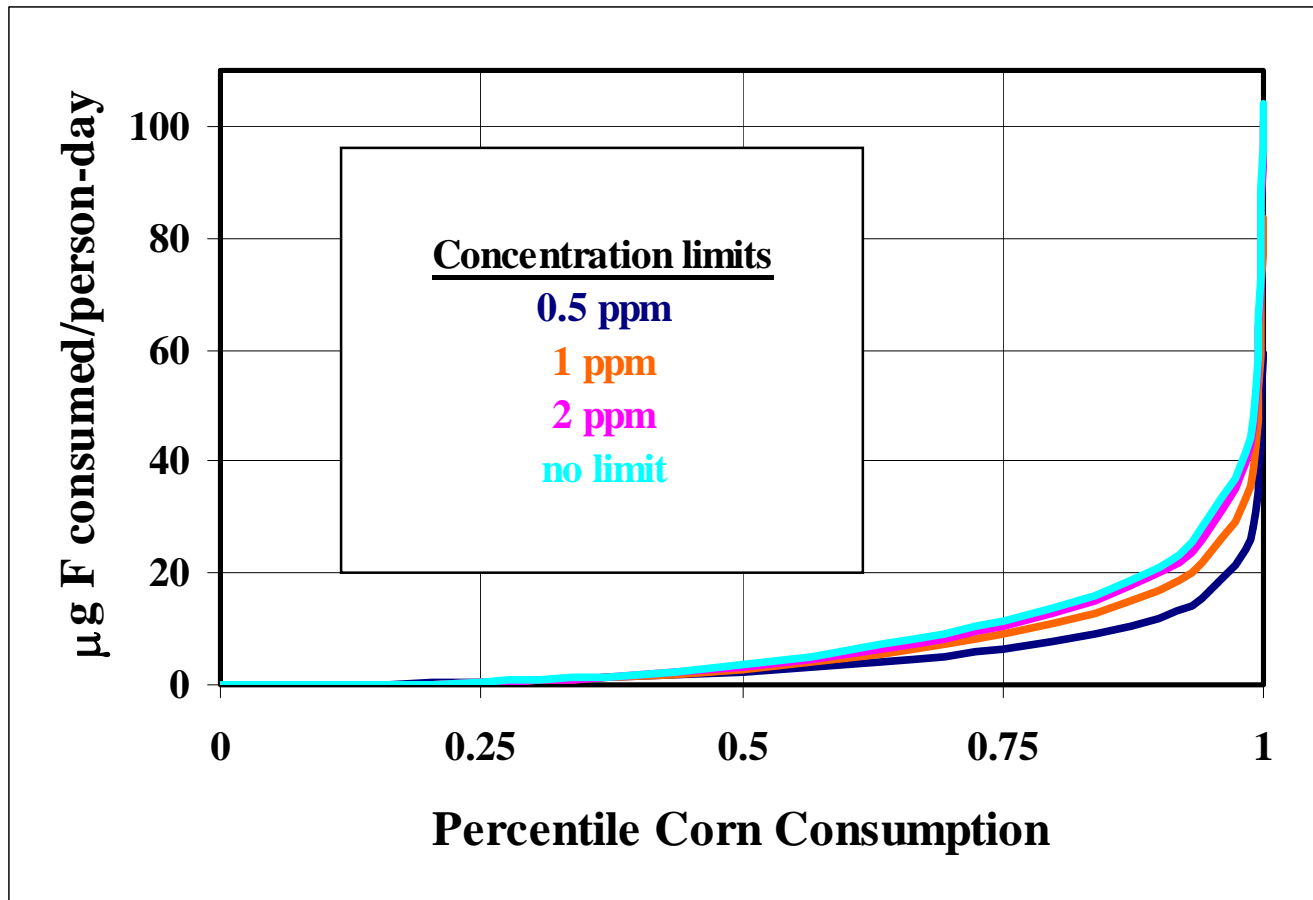
Average Presence in US Corn FDA surveillance data (1994-1995)

- Comparisons:
 - Non-detectable in Canada 1994, but 15,000 parts per billion (ppb) in 1993
 - 7,100 - 54,000 ppb in South Africa in 1992



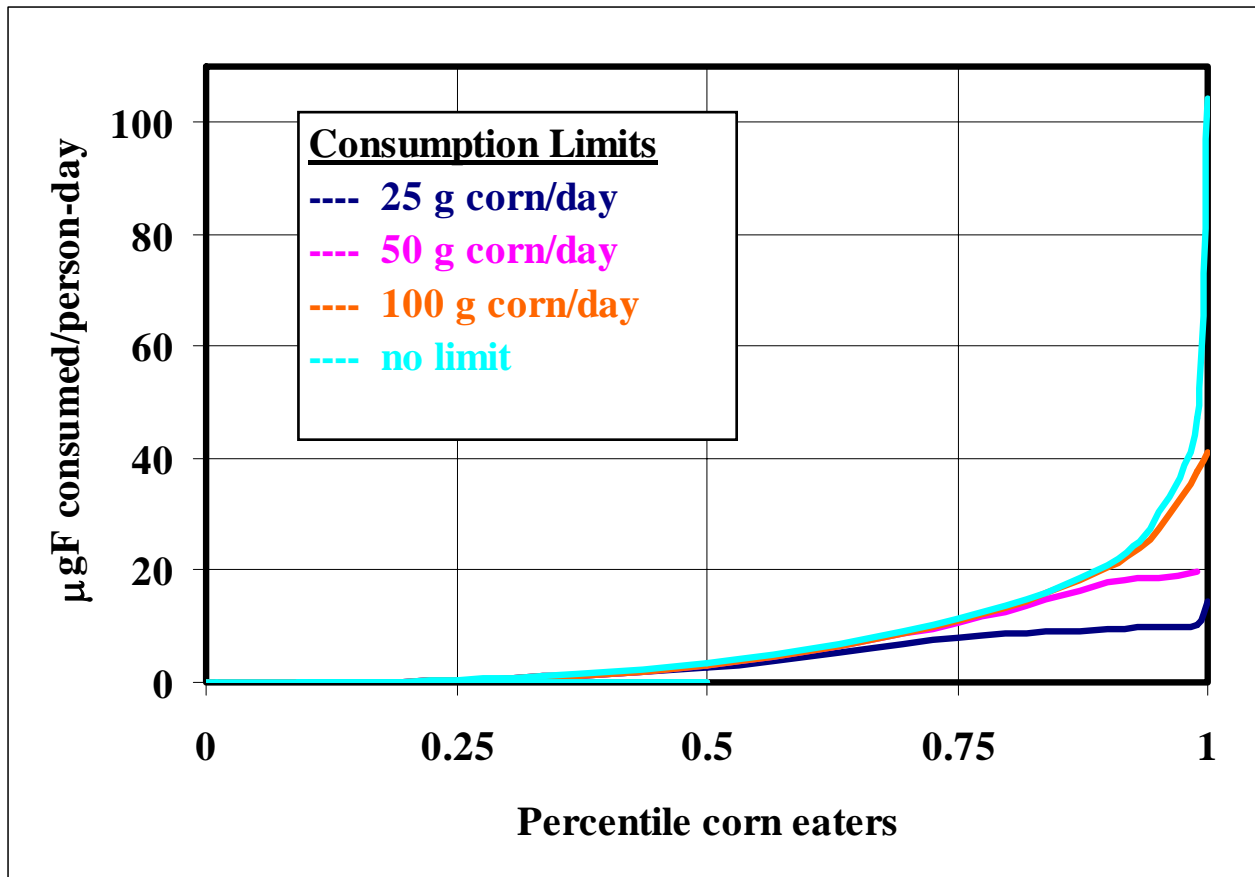


Exposure to Fumonisin (with concentration limits in corn)





Exposure to Fumonisin (with consumption advisories)





Dose/Response Estimate

- Variability in response to fumonisin:
 - This is the inner (variability) loop in the Monte Carlo
 - Costly and time-consuming to reduce this uncertainty
- Accounts for:
 - Extrapolation from rats to humans
 - Variability of the human response (e.g., due to differences in body weight)
 - Less than adequate data on dose/response

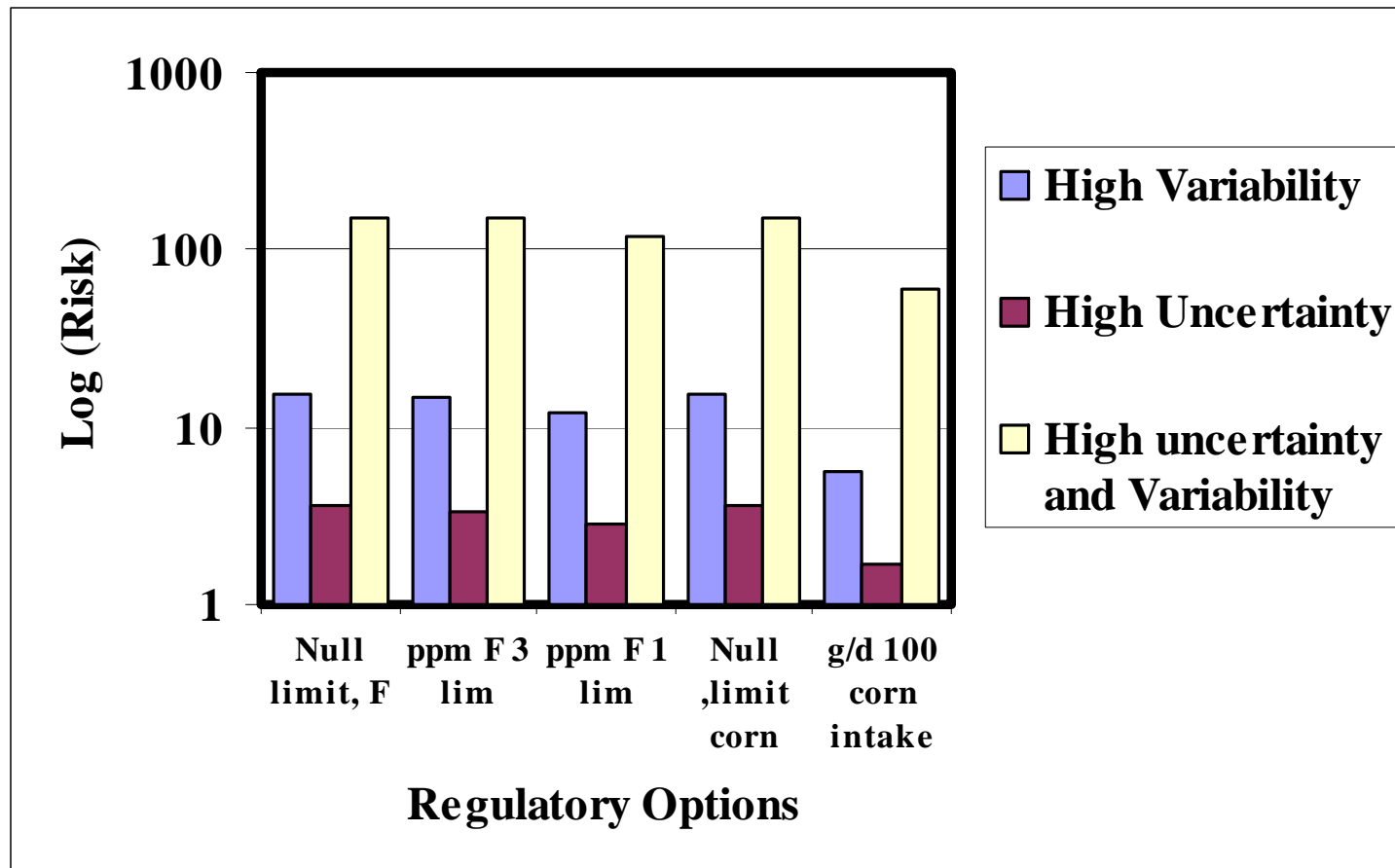


Estimation Issues

- **How to quantify the uncertainties about parameters like dose/response ratios:**
 - Expert opinion of risk from various levels of fumonisin, based on available toxicity information
- **Pathologist's rating scale for degenerative lesions in the kidneys:**
 - Runs from 0 to 3, with 1 being the smallest observable effect



Role of Uncertainty and Variability in Nephrotoxicity Risk





Graph Shows Value of 2-D Monte Carlo Uncertainty Analysis

- Research to reduce uncertainty can sometimes be worthwhile
- In this case, the variability contributes more to the overall risk than the uncertainty:
 - However, all values are low enough that further action is not needed



Risk-Management Options (reduce intake in population)

- Set limits on fumonisin in corn products:
 - Burden on producers
- Issue a consumption advisory:
 - Burden on consumers
 - Analysis shows this may be the preferred option
- Collect additional information on vulnerable groups:
 - Young, pregnant, poor, by ethnic group, by region
- Collect additional information on concentrations:
 - Where do high-concentration products come from?
 - Supply chain



Conclusions and Caveats

- Small risk and little reason for concern, providing that:
 - Consumption data is not heavily skewed to urban populations
 - Levels of fumonisin in corn crops exposed to drought conditions are included
 - Degenerative kidney lesions are the most sensitive human endpoint



Exposure in South Africa (Marasas, 1997)

- Urban dwellers:
 - 84 micrograms (μg) of fumonisin per person-day
- Rural dwellers, healthy corn:
 - 3,262 μg of fumonisin per person-day
- Rural dwellers, moldy corn:
 - 24,780 μg of fumonisin per person-day
- Compared to an estimated tolerable daily intake of 56 μg of fumonisin per person-day



Risk-Management Options (South Africa)

- Limit fumonisin in the corn crop to 0.5 ppm?
 - May reduce fumonisin in average diets, but only insignificantly (by 0.5 μg per person-day)
 - Wouldn't protect the most exposed consumers
 - May be unobtainable for subsistence population (import high-cost corn, or substitute another food)



Application to Foot-and-Mouth Disease

- Simulate outcomes of disease outbreaks for a variety of mitigation strategies:
 - Epidemiology models
 - Economic models
- Include variability (e.g., weather conditions) and uncertainty (infectivity, dissemination rate, airborne spread)



Additional Uncertainties

- **Two-dimensional Monte Carlo works well for uncertainty about the parameters of a model:**
 - But some uncertainties may be inherent in the models
- **Examples:**
 - The model assumes perfect compliance with concentration limits, but actual compliance is imperfect
 - The model uses a conservative estimate of toxicity
 - The model omits some endpoints or damage mechanisms



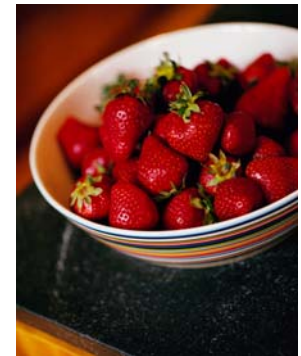
Model Uncertainty

- **Two-dimensional Monte Carlo works less well when some models do not include all relevant features**
- **“All models are wrong, but some are useful”:**
 - George Box
- **How can we reasonably assess the probability that each model is “correct”?**
 - Most (or all) are gross simplifications of the real world
 - Some are known to be conservative (or non-conservative)
 - Different animals represent different human toxic endpoints (for example, rats versus mice)



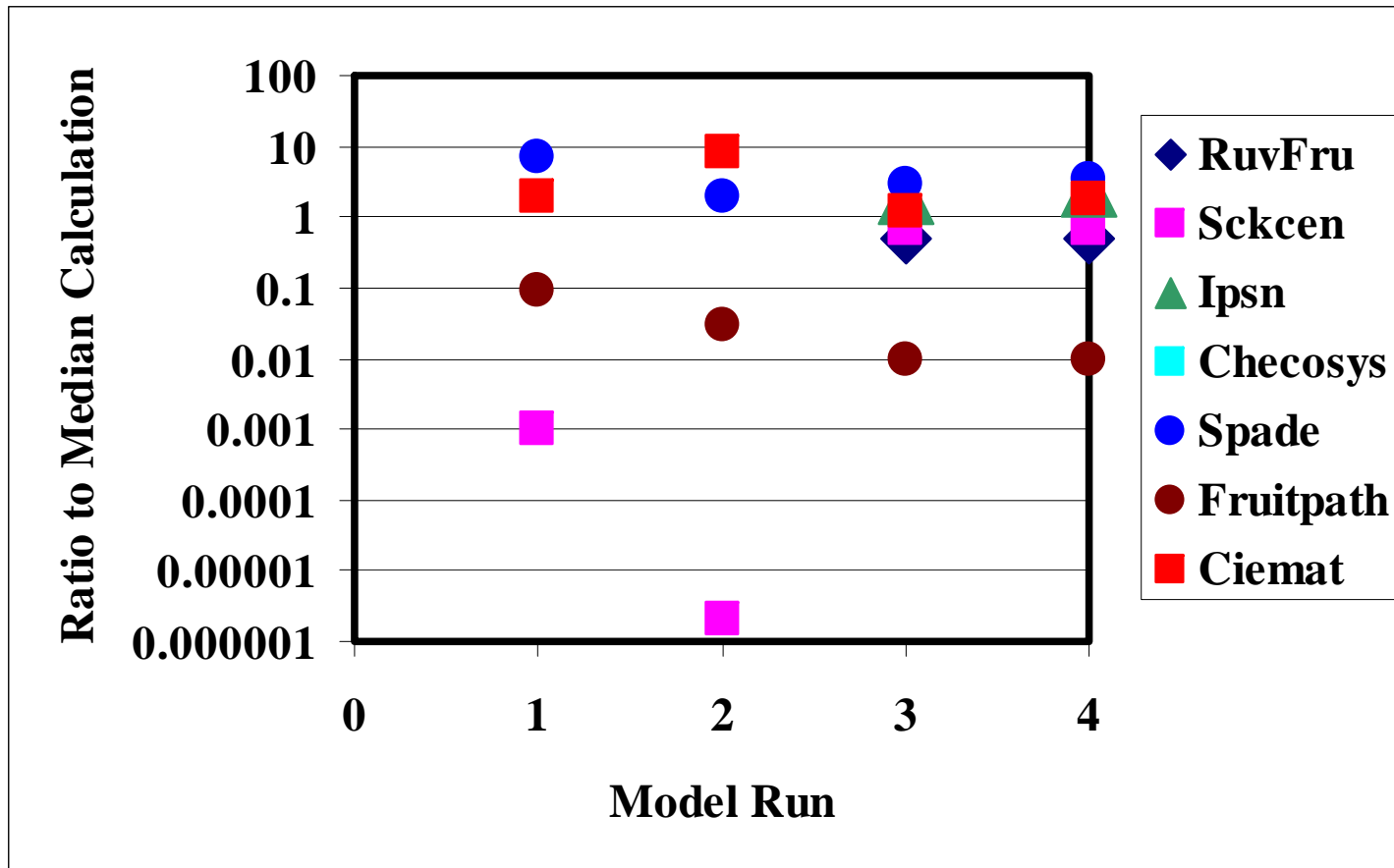
Model Uncertainty: Example

- Linkov and Burmistrov (2003):
 - "Model uncertainty and choices made by modelers: Lessons learned from the International Atomic Energy Agency model intercomparisons" in *Risk Analysis* 23(6)
- Modelers interpret problems differently, resulting in uncertainty:
 - Differences in problem formulation
 - Differences in model implementation
 - Different parameter selections
- Predictions from six models for cesium concentrations in strawberries differed by as much as seven orders of magnitude





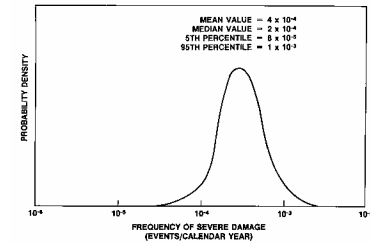
Six Model Predictions for Cesium Concentrations in Strawberries





Risk Communication

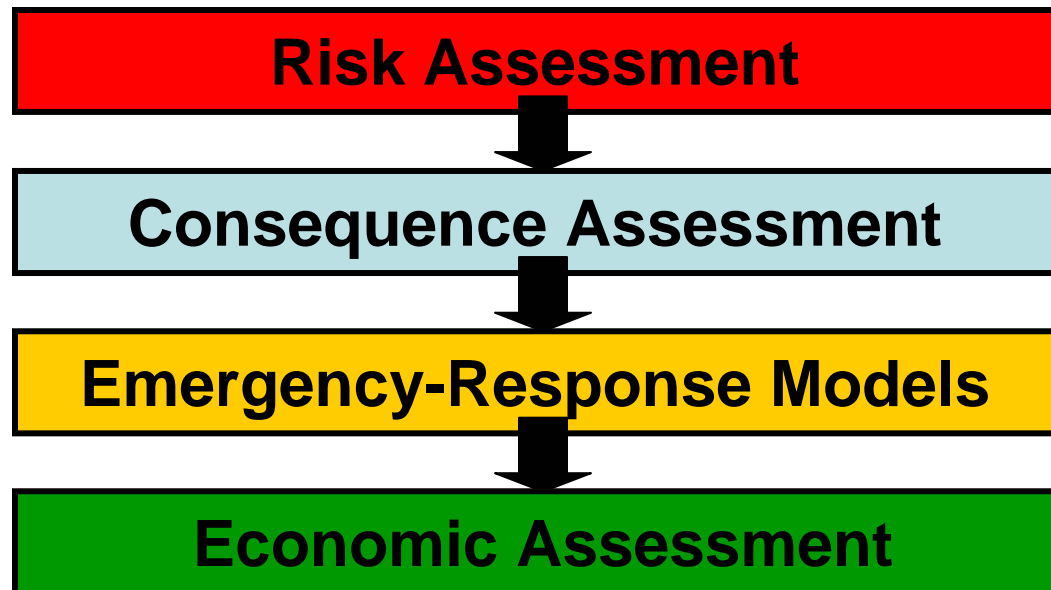
- **Probability distributions showing total uncertainty**
- **Pie charts showing contributions to overall uncertainty from different sources:**
 - Uncertainty versus randomness or variability
 - Particular areas of scientific uncertainty
- **Can shed light on value of information:**
 - Which uncertainties are important to resolve





Next Step in Decision Making

- **Assessment of stakeholder values:**
 - **As a basis for identifying the most desirable risk-management options**





Take-Home Messages

- **Two-dimensional Monte Carlo recognizes uncertainty about inputs to a simulation**
- **Once these are highlighted, research and data collection can reduce the uncertainty**