# Cognitive Demarcation in Assessing Food Risk in the E.U. and the U.S.: Melamine and Listeria

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## Introduction

In 1983, the National Research Council (NRC) issued a report that codified the basic paradigm of risk analysis in policy making (NRC 1983). Focusing on health related risks, it called for a clear separation of risk assessment from risk management. Risk *assessment*, the committee proposed, should embody the "scientific findings and judgments" of expert scientists. Risk *management*, on the other hand, the document stated, should reflect "political, economic and technological considerations." The separation of risk assessment and management was an effort to protect risk assessment from external (especially, political) interference and to bring it exclusively under the jurisdiction of the universalistic rules of science. In 1989, the guidelines were supplemented by a separate NRC study on risk communication that addressed the interface between risk analysis and society (NRC 1989). A third NRC report in 1994 consolidated the conclusions of both (NRC 1994). The NRC rules took root in the U.S. and became de facto global standards. International organizations, such as the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO) set out to implement the NRC's suggestions and so did other international and national organizations.

In the 1980s, across the world, a new research program appeared that has been interdisciplinary in method, critical in approach and global in focus. Several journals were launched that are devoted to risk analysis,[1] and there is now a burgeoning literature on the topic. Researchers in mathematics, statistics, the physical, biological, engineering and the social sciences, as well as the humanities stepped up to the problem of risk. At the most abstract level, probability theory, decision theory and statistics have tackled the most general, normative issues of how to handle ignorance and uncertainty. A large literature emerged in an attempt to formalize rules of risk assessment and create a universal methodology for a new science of decision making under uncertainty (Vose 2000, Rai et al 1996, Morgan and Henrion 1990.)

Yet, these universal standards also sparked controversies. As different risks are assessed by different scientific communities that draw on different methodologies and conventions, it is far from

[1] A few examples: *Risk Management*, *Health, Risk & Society*, *Human and Ecological Risk Assessment*, *Journal of Risk*, *Journal of Risk Research*, *The Journal of Contingencies and Crisis Management* and *Risk, Decision and Policy*. All of these were began publication in the 1990s. The international Society for Risk Analysis was founded in 1993.

clear if a one-size-fits-all approach to risk and uncertainty is possible or even desirable. Recently, efforts by the U.S. Office of Management and Budget (OMB) aimed at further standardizing risk assessment (OMB 2006) have been strongly criticized by an NRC panel (NRC 2007, see also Pate-Cornell 1996). Moreover, as the independence of the risk assessment process can be achieved in multiple ways, institutional differences will also create variation in the risk assessment process.

In this paper we will focus on one narrow area in risk analysis: food safety. Observing risk assessments responding to two recent food safety problems, melamine and listeria, by scientists in the U.S. and the E.U. we describe differences in the way each handled uncertainty.

Much of the risk literature that compared the U.S. and the E.U. focused on the question of precaution and addressed differences through the dissimilarities in "political culture" (Jasanoff, 2005, Murphy and Levidow, 2006). Some studies argue that Europe is more precautionary than the United States while others see little evidence that the E.U. is more averse to uncertainties. Yet most of this literature scrutinized the way risks are managed on the two sides of the Atlantic (Hammitt et al 2005, Lofstedt and Vogel 2001, Lynch and Vogel 2001, but see Millstone et al. 2008). In this paper, we shift the focus from risk management to risk assessment . We will analyze two cases of food safety hazards, melamine and listeria and point out the main differences in the way U.S. and E.U. expert panels handled uncertainties in their reports. We will argue that within the scientific world of food risk assessment, there are distinct scientific subcultures or epistemic cultures (Knorr-Cetina 1997) each with their own sets of methodologies (Debure, 2009, Demortain, 2008), standards and rules for dealing with uncertainty. We will address two of such subcultures: the worlds of chemical contaminants and biological hazards. We will offer as evidence the commonalities within the two hazards and differences across them to illustrate this point. Moreover, there is a different institutional structure in the E.U. and the U.S. that has consequences for the ways uncertainty is recognized and articulated. The E.U. model of risk assessment is centralized and it is based on collegiality and internal consensus, risk assessment in the U.S., on the other hand, is decentralized and more openly adversarial. As a result, choices about uncertainty will be different, because E.U. assessors face different pressures than those in the U.S.

In this paper, therefore, the argument has two moving parts: epistemic culture and institutional structure. These two, however, are not acting independently in an additive way but the second is nested in the first. The two together decide how risk assessors demarcate the causal boundaries of the problem they will set out to solve. These choices are themselves not scientific but they will decide what will count as knowledge and what will count as uncertainty.

## Role of Scientific Uncertainty

To create a solvable puzzle science must delineate the cognitive boundaries of its inquiry; it must simplify to make the problem manageable. This cognitive demarcation that lifts the problem out of its empirical context itself is not a scientific decision and it depends largely on what is perceived to be the problem at hand and the particular traditions of the scientific disciplines and subdisciplines participating in the analysis as different scientific communities follow different standards of proof and methodological rigor.

Risk assessors must answer causal questions because their report is input for intervention by risk managers. Even when their job is primarily descriptive and they have to assess only the extent of a problem, their estimates rely on causal mechanisms where causes (or consequences) can be used as indicators of the size of the problem. In food safety, to estimate the extent to which a contaminant is a health hazard, experts must understand the scenario, the causal process that delivers the contaminant to the human body and yet another causal mechanism through which it creates its harmful effects. To begin the investigation, experts must create a causal model that will separate relevant factors from irrelevant ones. Only relevant factors count towards uncertainty, irrelevant factors do not.

We discuss two acts of discretionary cognitive demarcation in the interest of problem management both are decisions on the boundaries of the causal model, and the choice of the limits beyond which ignorance becomes irreducible but irrelevant. The first concerns the tension between analysis that is built on isolation of causal processes (e.g. Shrader-Frechette, 2007) and the fact that the effect of individual hazards often depend on the synergistic presence of other agents. In other words, hazards interact with their context. The second addresses the common distinction between variability and uncertainty, the first being an inherent and irreducible characteristic of reality and as such requires no further investigation. Here the key is the decision where the causal chain begins.

The organization of the paper moves from more general considerations towards the more specific. First, we will explain the two types of discretionary cognitive demarcation. We will then turn to the differences between the world of chemical contaminants and biological hazards. This will be followed by the institutional differences in assessing food risk in the U.S. and the E.U. We then introduce our two case studies, melamine and Listeria monocytogenes. For each, we will give a short presentation of the history of the problem and then we point out the choices risk assessors made and how that influenced the amount of uncertainty they found.

## Analysis and Synergism

Since Francis Bacon's Novum Organum, the logic of scientific investigation has followed an analytic path. Analysis assumes that the best way to scientific discovery is through the isolation of individual causes (Hacking 1983, Shadish et al. 2002). Experimentation is a method to separate an individual causal factor from its environment and a carefully controlled experiment is built on the idea that the true effect of a cause is revealed when all other – confounding – factors are "held constant," i.e., they are removed from the causal process. This method assumes that causal influences are additive.

However, causal factors are often not additive but can interact in various ways. Synergistic effects are ones where causal factors enhance the effect of one another. Antagonistic effects occur when factors of opposite influences weaken each other more than one would expect on the basis of the sum of their opposing influence. Many health hazards are the result of synergistic effects (or the absence of an antagonist). The U.S. Environmental Protection Agency (EPA) has been struggling with this issue, especially in the area of pesticides and carcinogenic substances (NRC 1994 p.227-228).

> "Most of the data available on toxicant interactions are derived from acute toxicity studies using experimental animals exposed to mixtures of two compounds, often in only a single combination. The use of information from two-component mixtures to assess interactions in mixtures containing more than two components is difficult from a mechanistic perspective. Studies of mixtures with more than two chemicals are rare and difficult to interpret. (EPA 1993, 6-12.)

Because binary synergism is still tractable the EPA considers data only on binary interactions and builds its models of more complex chemical mixes from pairwise evidence (EPA 2000, pp.90-103). Synergistic interactions increase the complexity of a problem considerably. It is not just the relative proportions of the mixture that becomes a new factor but also the conditions under which the elements combine or fail to do so. And once the possibility of synergism is entertained, the number of potential interactions quickly multiplies.

The importance of synergistic effects was reinforced by the NRC in 2007:

> "When agencies ask whether a particular chemical or technology causes or contributes to a particular disease, completeness in a scientific sense may entail consideration of evidence regarding the causative role of other factors in producing the disease of interest. For example, an assessment of radon exposure and lung cancer may need to consider the role of cigarette smoking as a potential confounding factor that influences the estimated risk of radon. Alternatively, the evidence on smoking may suggest that the risks of radon are larger for smokers than non-smokers, a so-called risk-modifying or synergistic factor. The scientific process of considering confounding and/or synergistic factors may assist policy makers in developing a broader sense of how risk can be reduced significantly and the range of decision options that need to be considered if maximum risk reduction is to be achieved." (NRC 2007 p. 135)

Synergism is a special case of the larger problem of context. To what extent should studies consider the entire context of a hazard is a difficult decision. No one ever eats melamine or listeria bacteria alone, but contaminants, be those chemical or biological, are eaten with particular foods (called the food matrix), which include other chemicals and/or organisms. Moreover, each food item is one element of a wider diet, which, in turn, is a part of a life style (exercise, smoking, stress etc.) and exposure to non-dietary environmental influences such as air quality, various diseases etc. In certain contexts, the hazard of concern may be completely harmless, in others, its adverse effect can be triggered or amplified. However, as important as context may be, including more context carries a price as it decreases the comparability of cases while it increases their complexity.

## Epistemic Uncertainty vs. Aleatory Variability

One of the fundamental distinctions deployed in risk analysis is the 1980s is the one between variability and uncertainty (Bogen and Spears 1987, Hattis and Anderson 1999, Hattis and Burmaster 1994, Nautta 2000). In recent official documents on risk analysis the two terms are always used in tandem and there is persistent call to make and quantify this distinction in risk analysis of all kinds (e.g. OMB 2006).

The contrasting definition of the two is seemingly straightforward. The U.S. Department of Agriculture Food Safety and Inspection Service (FSIS) risk assessment defined variability as "a description of differences among the individual members of a series or population." Uncertainty, on

the other hand, is "an expression of the lack of knowledge, usually given as a range or group of plausible alternatives" (USDA/FSIS 2003b xxx.), hence its nature is epistemic.

To muddy the definition somewhat, variability is often thought of as a form of uncertainty understood in a more general way. Variability is a part of uncertainty analysis and it is used to calculate uncertainty factors and estimates. Because, we are not supposed to be able to reduce variability by obtaining new information that would make it predictable and understandable as we can with uncertainty, one has to answer the question: what creates variability? Variability is supposed to be aleatory (as opposed to epistemic), in other words, it is said to be completely random. Some treatments of the subject invoke quantum mechanics and Heisenberg's famous uncertainty principle to illustrate this point (Vose 2008 p.48.). It is, therefore, surprising to find that the OMB demands in its 2006 risk assessment guidelines that "Where feasible, characterization of variability should […] disclose and evaluate the most influential contributors to variation in risk" (OMB 2006 p.16). Aleatory factors have no discernible contributors. By the common definition, only epistemic uncertainty has knowable causes.

It requires only a little reflection to see that the starting point of any risk assessment is, in fact, variability: some people get sick, others do not, some chemicals or organisms are pathogenic, others are not. The uncertainty that research must address is about the reason for this variability. If we know what caused the variable outcome (health or sickness) or which of the varied causes are responsible for a particular outcome (sickness) we need not worry about uncertainty. If we want to predict individual outcomes, we can do that with the help of other variables which must have variability themselves and their variations must correlate with the variation to be explained. For instance, we may find that a sickness attacks only small children. We can use the variability in age to explain variability in sickness by creating more homogenous subpopulations. In this case, adding a piece of information about each person (age) would decrease uncertainty. On the other hand, if we found that the conditional probability of listeriosis is constant (does not vary) across age groups we would be left with all the uncertainty we had before we started our investigation.

When does variability carry uncertainty? It does when our knowledge is about the aggregate population but we want to predict individual outcomes. But it carries no uncertainty when we are faced with the opposite problem, when we know the individual outcomes and want to predict the

population value. If all we care about is the total amount of contaminants in foods on the market, by summing the variable individual values, we can calculate that without uncertainty.[2]

Whether variability is a source of uncertainty depends on what we want to explain and how, in other words, it depends on our explanatory model. As a NRC panel pointed out in the context of seismic risk discussing a report by the Senior Seismic Hazard Analysis Committee [SSHAC]

> "SSHAC correctly points out that the classification of uncertainty as epistemic or aleatory depends on the model used to represent seismicity and ground motion. […]A reasonable interpretation of the probabilistic models used in seismic hazard analysis is that they represent not intrinsic randomness but uncertainty on the part of the analyst about the actual states and laws of nature—for example, about the number of earthquakes of magnitude 6 to 7 that will occur in the next 50 years in a given crust volume. According to this interpretation, all or most of the uncertainty in PSHA [Probabilistic Seismic Hazard Analysis] is due to ignorance. In certain cases, uncertainty due to ignorance may be expressed numerically by long-term relative frequencies. […]. . . Even though we have discussed probabilities appearing in the model of the world and the epistemic model, and we have given them different names, leading philosophers of science and uncertainty (e.g. de Finetti 1974; de Groot 1988) believe that, conceptually, there is only one kind of uncertainty; namely, that which stems from lack of knowledge.
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> Other statements support this position. For example, Section 2.2.6 states that ". . . the different terminology [aleatory versus epistemic] is not intended to imply that these uncertainties are of fundamentally different nature." Similarly, Section 1.8 points out that in the context of seismic hazard analysis, "the division between the two different types of uncertainty, epistemic and aleatory, is somewhat arbitrary." **The panel concludes that, unless one accepts that all uncertainty is fundamentally epistemic, the classification of PSHA uncertainty as aleatory or epistemic is ambiguous."** (SSHAC 1997 pp.32-3 emphasis in the original)
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> Three years later, the NRC concluded:

[2] Assuming perfect measurement, a complete census of all individual food items and that aggregation is additive.

> "Although the distinction between natural variability and knowledge uncertainty is both convenient and important, it is at the same time hypothetical. The division of uncertainty into a component related to natural variability and a component related to knowledge uncertainty is attributable to the model developed by the analyst. Consider flood frequency. In the future—at least in principle—the sophistication of atmospheric models might improve sufficiently such that flood time series could be modeled and forecast with great accuracy. All the uncertainty currently ascribed to natural variation might become knowledge uncertainty in the modeling, and thus reflect incomplete knowledge rather than randomness. ***Modeling assumptions may cause "natural randomness" to become knowledge uncertainties, and vice versa***. In its risk analysis framework, the Corps should be clear about which variables it treats as natural variability, which it treats as knowledge uncertainty, and why and how it makes this distinction." (NRC 2000 pp.42-3, emphasis added.)

The uncertainty and variability distinction is a matter of convenience and practical choice. One could claim that whatever variation is left at the end of the investigation, even if we suspect that it is related to variables missing from our model, could be treated as if it were natural or aleatory. Yet this is would make variability a special form of model uncertainty.

## Comparing the Risk Assessment for Chemical Contaminants and Microbiological Hazards

Most risk assessment documents in food safety follow a standard format with four parts. They begin with hazard identification where the report establishes the adverse health effects of consuming food contaminated with the pathogen. They then move to exposure assessment that estimates the frequency and level of the pathogen by ingestion of contaminate foods. Here the report must establish the amount of pathogens in the environment and the various scenarios through which the pathogen reaches people. The third step is called hazard characterization. Here the question is what happens once the pathogen enters the human body. This step develops a dose-response model to see how much of the pathogen is necessary to result in sickness. Finally, risk characterization assesses the overall adverse effects of the hazard on the entire population and certain subpopulations.

Even though their reports are structured similarly, chemical contaminants and biohazards are two separate worlds and their risk assessments follow different methodologies, rely on different scientific communities and standards and their experts are institutionally separated.

The analysis of chemical contaminants relies heavily on experiments on animals conducted in laboratories. The main aim of chemical risk assessment is to establish a single safety threshold of intake. Because the same chemical can be metabolized differently, a different Tolerable Daily Intake (TDI) can be established for different subpopulations. Microbiological risk assessment emerged in the mid 1990s. It was an effort to extend the tools of risk analysis developed and used in chemical, engineering, physical and nuclear risk to the area of food hygiene, but it was obvious from the start that assessing microbiological hazards require its own methods (Hathaway and Cook 1997, Post 2006). [3]

Unlike chemicals that are usually stable and inert, biological hazard are live organism that can reproduce, grow and die. As microbiological pathogens come in several strains, one biohazard can be de facto several hazards, some highly virulent others quite innocent. Because hazard agents are rarely observed at the moment of ingestion but are measured in the food at an earlier time point, calculating exposure and dosage poses a far greater task for microbiological than for chemical hazards. To get from observed levels of biohazards to dosage taken by people, scientists must consider the pathogen's entire career as it travels from its origins through different environments to the point of contact with humans. This is the reason why microbial pathogens are almost always assessed in a specific food item (listeria in deli meat or salmonella in eggs etc.). By limiting the context to a single food group the risk assessors can reduce contextual complexity. The artificial environment of the laboratory often tells us little about the natural development of these microbial organisms and scientists must rely on surveys and mathematical models to estimate the amount of biohazard people ingest. Furthermore, individuals have different levels of susceptibility depending on digestion (stomach acidity, or the quality of their intestinal mucosa) and immune systems. Chemicals too vary in how they metabolize in the body but those mechanisms are often captured quite well by toxicokinetic models developed from animal experiments.[4]

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[3] The new field of microbiological risk assessment also had to create its own data. It needed quantitative measurements that were not available because earlier forms of food hygiene management relied on more qualitative information.

[4] In fact, the EU, the US and the WHO/FAO all have separate guide documents for risk assessment in these two areas.

To understand the health effects of biohazards, one must know about a lot of contextual factors including the types of food items the pathogen is attached to as this may influence its growth and virulence and the food matrix, the kinds of foods co-digested with the pathogen. These interactions can be far more important than the laboratory "net" effect of the pathogen or its initial concentration in the food. Risk assessments often do not seek to establish a TDI but they aim at identifying dangerous food items, conditions or susceptible populations.

Expert panels are set up separately. The chemical contaminant panels are mostly dominated by chemists, toxicologists, while biohazard experts tend to be microbiologists, epidemiologists, hygienists and statisticians.

## Comparing the Risk Assessment Process in the E.U. and the U.S.

The U.S. and the E.U. devised two different ways of protecting the scientific autonomy of risk assessment called for by the NRC in 1984. In the U.S., risk management is not separated institutionally from risk assessment, as it is in the E.U., the regulatory agency carries out much of the research itself, but the overlapping jurisdictions of multiple risk management agencies and the utilization of external peer review and full transparency protects risk assessment from direct political influence.[5] In the E.U., the same goal is achieved differently by organizational and bureaucratic insulation.

In the E.U., the European Food Safety Agency (EFSA) is the central agency for assessing food risks. While each member state has its own food safety agency, EFSA is an independent organization with an E.U.-wide mandate. EFSA has its own permanent and ad hoc panels that are convened to produce risk assessments on request from the European Commission Directorate General for Health and Consumers which is responsible for risk management in the E.U. The microbiological hazard (BIOHAZ) unit receives assignments related to biological hazards such as Listeria monocytogenes in RTE food, and the chemical contaminant (CONTAM) unit is responsible for assessments related to food and feed contaminants such as melamine in food items and residues of veterinary drugs. Risk management is carried out by the European Commission. In the E.U., the separation of risk assessment and risk management is not just conceptual, but also institutional. EFSA is not charged with risk management and the EC does not participate in risk assessment.

5 This protection, as everywhere in the world is relative and in specific cases can be inadequate.

In the U.S., there are several federal agencies that have overlapping responsibilities for food safety at the federal level. The most important ones are the Food and Drug Administration (FDA), the U.S. Department of Agriculture, the Environment Protection Agency (EPA) and the Centers for Disease Control (CDC). These agencies are entrusted with both risk assessment and management tasks and their jurisdictions are often separated by historical accidents rather than clear, functional logic. These regulatory agencies have their own research divisions. The FDA has its Center for Food Safety and Applied Nutrition (FDA/CFSAN) and the USDA its FSIS. The Environment Protection Agency carries out its own food related risk assessment mainly concerning contaminants found in water. Biological hazards are mostly within the jurisdiction of the FDA and USDA, while contaminants belong to the FDA and the EPA.

Cooperation with external institutions is organized very differently in the E.U. and the U.S. In the E.U., EFSA's interactions with external organizations engaged in risk analysis is confined to delivering grants to pre-defined partner organizations nominated by member states in order to carry out preparatory work or data collection for the development of its scientific opinions. In the U.S., federal agencies are not the only ones carrying out risk assessments. Many are undertaken by universities, single scientists or private research institutions on contract. The number of "complete" risk assessments is much lower than in the E.U., since a risk assessment process is launched only when the agencies decide that there is insufficient scientific information and they cannot depend on existing studies for their management tasks.

In the U.S. a collaborative approach between different agencies, industries and academia prevails, not only for risk management but also for risk assessment. In 1997, a food safety initiative was launched that called for collaboration between regulators, stakeholder, federal agencies, states and the various risk assessment organizations. A risk assessment consortium (RAC) was created to coordinate the activities, promote scientific research and share information. [6] The RAC participates in reviewing draft risk assessments, and the review system in the U.S. is active at different stages of the development of a risk assessment report. The review process includes public meetings and public comments, internal reviews from the agencies, and peer reviews addressed to specific reports.

For example, the FDA/FSIS risk assessment on Listeria monocytogenes in ready-to-eat foods begun in January 1999. In May and September 1999, following public meetings in which the

[6] The RAC includes eighteen organizations under the FDA, USDA, EPA, CDC, National Institute of Health (NIH), National Marine Fisheries Service (NMFS) and the US Department of Defense (DOD).

"public" and the National Advisory Committee on Microbiological Criteria for Foods[7] participated, comments on scope, data, risk assessment approach and assumptions were requested. A few months later, members of the RAC were asked to review and discuss the draft risk assessment document, and the FDA reviewed the model that had been developed. The review task was then passed on to selected FDA risk managers and later to selected government experts and special government employees. A quality assurance team within the FDA verified the data, and in autumn 2000 an interagency review by the FDA, FSIS and CDC was carried out. Early 2001, a new public meeting was held where the results were presented and new comments were solicited. FDA and FSIS reviewed these new comments and revised document. In 2003 the revised risk assessment was made available and the results were presented at a public meeting. Another, companion risk assessment on Listeria monocytogenes in deli meats (FSIS 2003b), prepared by a professor of the Virginia Polytechnic Institute and two members from the FSIS/USDA risk assessment division, which concentrated on meat processing plants was reviewed by experts within the USDA, from other governmental agencies (Health Canada), from academia and from a private risk consulting firm.

The review system allows access to the details of the document to a wide variety of commentators. Although public comments and peer review can address the same issues (data, assumptions, models), the former is widely open to stake holders, whereas the latter involves a set of selected experts, who are not necessarily by the agencies involved. Both public and peer comments are published, often as part of the final document.

In Europe, the review system remains mainly internal. The selection of the panel members are guided by a set of rules that considers not just qualifications but also a balance of geographical region and gender. While conflicts of interest must be disclosed in each case, principles of transparency are tempered by considerations for confidentiality. The work is conducted inside the working groups. The risk assessments (or more generally "scientific opinions") are prepared by working group members. The working group consists of a few members of the unit's expert panel joined by other invited scientists plus EFSA staff from the unit to support the work. At each meeting, the work done is presented to the unit's expert panel and once finalized the panel has to adopt or reject the opinion. All panel members can comment on the work prepared. In addition, an *ex post* quality assurance process exists, that conducts a general review of already-adopted opinions. The conclusions and recommendations are reported in the final annual report of EFSA's quality

[7] It was established in 1988, in response to National Academy of Sciences' recommendation for interagency approach to microbiological criteria for foods and it provides advice to federal food safety agencies.

manager. Disagreement stays within the working group and the final document is a result of a consensus, although in rare cases minority opinions are submitted. The work is available to the public only once it is finalized.

EFSA usually solicits outside opinions only for guidance documents on methodology or on its process of selecting panel members and not on particular cases.[8] One exception is the peer review process of active substances used in pesticides, where usually one member state receives the initial dossier from the manufacturer to carry out the initial risk assessment. The resulting report is sent to EFSA, and it is made available for 40 days for public comments. Then scientists from the Pesticide Risk Assessment Peer Review (PRAPER) unit and member states carry out a peer review of the report. The conclusions are then sent to the European Commission which decides to authorize or reject the active substance.

From a U.S. perspective the European process seems alien. In a comment submitted to EFSA by the U.S. Office of Management and Budget on EFSA's guidelines on transparency in risk assessment, the OMB wrote:

> In the discussion of transparency, there is one area that is not mentioned at all and that is transparency regarding the level of external independent expert review and public comment. It would be helpful if the EFSA assessments provided mention of the level of external review any assessments may have had. In the U.S., we typically have public comment as well as external peer review as in general, we find that public comment is not a substitute for the knowledge gained from having an independent external peer review. A transparent discussion of both the public comment process and external review process that each document has undergone would be helpful. For discussion of expert review, the following OMB bulletin on peer review may be helpful: http://www.whitehouse.gov/omb/assets/omb/fedreg/2005/011405_peer.pdf (EFSA 2009b, p. 7)

[8] E. g. Public consultation on the Scientific Committee's "Guidance on human health risk benefit assessment of foods" , the GMO Panel's "draft guidance document for the environmental risk assessment of genetically modified plants", the Plant Health Panel's "guidance document on a harmonized framework for pest risk assessment."

While scientific risk assessment in the U.S. is decentralized, collaborative, open and adversarial, in the E.U., it is a centralized, bureaucratic, internal and collegial process. Protected by its rules of operation, EFSA can produce far more reports than its U.S. counterparts together.[9]

## Melamine

### Background

In 2007, responding to reports of sickness and deaths of pets in the U.S., an investigation was launched by the FDA that found that wheat gluten, an important nutrient in pet food, was tainted with a chemical contaminant named melamine. Melamine, an industrial chemical used in plastics and cleaning products, causes various adverse health effects, the most important of which is the formation of crystals or bladder stones in the kidney leading to renal failure. Melamine, which is rich in nitrogen, was added to animal feed to boost the apparent protein level which is usually estimated by measuring the nitrogen content of the product. The U.S. investigation quickly located the source of the contamination. All cases could be traced to Chinese imports. The first, interim report was issued by the Food and Drug Administration on May 7, 2007 with an update released on May 25. This was followed by a peer review from six scientists on June 7.

The first risk assessment document by the European Food Safety Agency (EFSA) was issued the same day and was amended on July 4. The document labeled "provisional statement" reviewed the available evidence and relied heavily on the FDA documents (EFSA 2007a p.2).

Concern about melamine surged again in the fall of 2008. On September 11, protein faking melamine was reported to be found in milk powder used in baby food in China. At least six children died and over 50,000 were hospitalized with severe kidney problems. The news of infant deaths in China gave new momentum to the investigations. EFSA produced a new risk assessment document on September 24, 2008, paying special attention to milk powder related products (EFSA 2008). The FDA issued an interim report with a similar focus on October 3 and an update a month later. This update was peer reviewed next June (FDA 2009). The two agencies, while working separately, clearly kept an eye on what the other was doing, but while the EFSA documents reference the work done by the FDA, the U.S. reports do not mention EFSA, not even in the fall of 2008, when EFSA was quicker with its response.

[9] Yet another reason why the joint risk assessment output of all US federal agencies in food safety is just a fraction of EFSA's is the much more active role courts play in the US in creating and enforcing safety rules.

## Risk Assessments

### Process

The processes that produced the risk assessment documents in the U.S. and Europe were different. In the U.S., the FDA reports were submitted to public peer review. The first panel of experts in 2007 were hand picked by FDA and they were asked to answer ten questions about the report including whether uncertainties are properly addressed, whether relevant data were ignored, whether the methodology was appropriate etc. The response to each question was recorded for each panelist with a rejoinder from the FDA. The 2009 panel was selected differently. The FDA contracted Versar Inc., a private company that selected the expert panel. This time, the panel was given 12 questions and an additional prompt for "specific observations." The peer review and public criticism from experts developed risk assessment as a quasi-public adversarial process

The EFSA documents on the other hand were the products of committees designed to contain disputations within the boundaries of the expert body. The EFSA reports were manifestations of the scientific consensus reached by the experts. This consensus then counted as the final word at the time.

### Content

In many ways the risk assessments EFSA and the FDA produced in 2008 were quite similar, but there were some important exceptions. Both worked from the same research data, both identified similar problems with the available scientific evidence and both considered the worst case scenario for exposure in the absence of reliable data. Each commented on the difficulty to estimate long-term, cumulative effects, and both noted the fact that there was little data on melamine analogues such as cyanuric acid, ammelide and ammeline, and both used the known qualities of melamine to estimate the toxic potency of the analogues.

In the risk assessment conducted by the FDA one central concern was the health of American infants as the U.S. did import milk products from China and contaminated Chinese milk powder could have been used in U.S. manufactured infant formula. The E.U., on the other hand, had banned the importation of Chinese milk and milk products and EFSA could be confident that no infant formula with Chinese ingredients was sold in the E.U.. Other food items, however, such as biscuits and chocolate products were imported from China and many of those contained milk powder.

The chief purpose of the two risk assessments was to establish a threshold above which exposure to the substance poses a health risk. Both documents presented a Tolerable Daily Intake (TDI) for humans but here they diverged considerably. The FDA arrived at a TDI of 0.063 mg/kg bodyweight per day, while EFSA deduced a much higher 0.5 estimate. The reason for the discrepancy was due to one factor of uncertainty absent from the EFSA calculations but emphasized by the FDA. The problem was that while data on the effect of melamine were available, and the experts felt that the effect of its analogues could also be estimated, there was no research on the combined effect of these contaminants. There was a strong suspicion based on limited evidence from pets that their effect is not additive but synergistic and their combination enhances crystallization in the kidney. Giving consideration to uncertainty about synergistic effects, the FDA revised its TDI estimate from its 2007 report. The earlier TDI of 0.63 mg/kg bodyweight per day was adjusted by a 10-fold safety factor and was set at 0.063. EFSA, on the other hand, arrived at a 0.5 mg/kg TDI by ignoring this uncertainty (EFSA 2008).

The final figure the FDA presented, in fact, included two different calculations: one for infant formulas using milk powder, and one for all other foods. These two calculations, however, yielded the same final number but for different reasons. In its October 2008 Interim Report the FDA presented the final 0.063 figure, but exempted infant formula from it.

> "The previous assumptions that U.S. FDA made in the 2007 risk/safety assessment regarding the pet food contamination episode cannot be applied to the current situation because the contaminated product represents the totality of caloric exposure for most of these infants; the exposure is chronic over months; the persons ingesting the products are infants and toddlers whose renal systems are not yet fully developed; and the exposure is not mitigated by previous passage through the digestive system of an animal. Moreover, several significant gaps in our scientific knowledge about melamine and its analogues toxicity regarding infants exist, including:
>
> 1. The impact of the presence of more than one melamine analogue which has the potential to increase the toxicity of the adulterated infant formula.
> 2. The consequences of continuous use of these infant formulas as sole source of nutrition.
> 3. The possibility that these formulations can be fed as the sole source of nutrition to premature infants with immature kidney function and even greater intake of infant formula per unit body weight for a longer time period than term infants.

> Thus, the U.S. FDA cannot establish a level of melamine and its analogues in these products that does not raise public health concerns." [FDA 2008a]

The FDA could have added uncertainty factors to account for these concerns, but, in essence, what it said was that the only TDI it could calculate would be overly alarmist, and therefore, for the time being, it would abstain. It took another month to produce a TDI for infants. In its November Update, the FDA wrote:

> "Because FDA has found infant formula where just melamine or just cyanuric acid was present, it is updating the safety/risk assessment. These findings were in U.S.-manufactured infant formula products, and only extremely low levels of melamine or cyanuric acid have been detected in them." (FDA 2008b)

The new finding, that synergism may not be an issue for U.S. manufactured infant formulas because they have either just melamine or just cyanuric acid, allowed the FDA to remove synergy from consideration for that class of products.[10] By crossing out the first source of additional uncertainty, the panel was left with the last two.

> "Infants may be more sensitive than adults to exposures because, for example, infant formula is the sole source of nutrition, exposure continues for up to 12 months, and renal function may be more immature compared to adults. This raises a high degree of uncertainty with regard to the determination of safety/risk. Given these conditions, FDA has applied an additional 10-fold safety factor, yielding a combined safety factor of 1000-fold, to compensate for these uncertainties. This results in a TDI/10 of 0.063 mg melamine/kg-bw/d." (FDA 2008b)

Synergism, a theme raised by several of the reviewers was a central concern for the FDA and it needed data to exempt one class of products.

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[10] The FDA did not address the possibility that melamine analogues from sources other than the formula, for instance in plastics, may combine with the contaminants present in the formula.

EFSA, on the other hand, says nothing about synergism in its 2008 report (EFSA 2008). It is curious that it was clearly aware of the problem as a year earlier, in its 2007 review, most likely following the earlier FDA report, mentions it in the context of pet food:

> "A source of uncertainty is the combined toxicity of melamine and cyanuric acid and their possible synergistic effects in relation to the recently observed toxicity linked to the acute renal failure and death of pet animals (cats and dogs) in the U.S. This mechanism is currently under investigation." [EFSA 2007a p.9]

Yet, this concern disappears from the 2008 report altogether resulting in a less conservative estimate of what level of melamine people can be exposed to. In fact, the document responds to a request to investigate melamine only, and its analogues are not mentioned in the initial charge. This made it easier to avoid the issue of synergism. Given the short time (about ten days) EFSA had to draft its risk assessment, this simplification must have been especially welcome. Yet, it is clear that EFSA could still have flagged the issue in its report to signal the additional uncertainty posed by the presence of melamine analogues that can make the effect of melamine much worse requiring a lower TDI. EFSA decided that it could ignore the synergistic effects, in fact, dealing with one important uncertainty by placing it outside the boundaries of its brief.

The problem of synergism is a profound one and represents a major methodological challenge in food safety research. The area of food contaminants are dominated by chemists, bio-chemists, toxicologists deeply immersed in a scientific methodology that puts heavy emphasis on experimentation and thus tends to view hazards from a context independent and additive approach. Treating melamine analogues as different hazards, the EFSA panel was following normal procedure. The lack of external review made it easier to ignore the synergistic effect.

The FDA decided to tackle the synergism issue, but once, context was acknowledged and synergistic effects were allowed, the quest for causal certainty became much more difficult and an infinite number of potential synergistic factors were possible to consider.

As in a 2009 peer review, one of the reviewers (Reviewer #1) of the 2008 FDA report commented:

> "Other substances that might have a synergistic relationship with melamine to cause disease are not identified in the S/RA. Is there certainty that other environmental or dietary

substances would not interact with melamine to potentiate the harm melamine causes or the possible harm the other substances could cause?" [FDA 2009]

Having to worry about all plausible combination of "environmental and dietary substances" expands uncertainty considerably. Moreover, it is not just that other materials could amplify the effect of melamine, but the ill effect of melamine could be that it enables or enhances the toxicity of other contaminants. Another FDA reviewer (#4) gave examples of chemicals for which melamine and its analogues can "act as a catalyst" or as "an absorptive site." [FDA 2009]

Neither EFSA, nor the FDA discussed the variability vs. uncertainty distinction. The word "variability" does not occur once in the risk assessments, although in the peer-review document, questions about intra- and inter-species variability[11] are raised and discussed. In fact, uncertainty in the melamine case was handled by using simple conventions about quantifying uncertainty. These uncertainty factors that modify initial estimates by dividing the allowable minimum pushing it downward are based on custom and are used in a manner that seeks to eliminate uncertainty as the implication of the TDI calculated with the help of the uncertainty multipliers is that the resulting value is certainly safe.

The comparison of the two cases show, that how the demarcation of the scope of the problem plays a key role deciding the amount of uncertainty experts report. Because the EFSA risk assessment concentrated on melamine alone it could dispense with the uncertainty of synergistic effects. To do that, the panel could rely on the usual convention of their experimental tradition that treats hazards individually and in an additive manner. The FDA, by opening up the Pandora's box of synergism, a concern emphasized by both its 2007 and the 2009 peer review, increased uncertainty.

## Listeria

### Background

Listeria, named after the English surgeon Joseph Lister, is bacterial genus and one of its seven species, Listeria monocytogenes, is frequently found in soil, water, vegetation and the gastrointestinal tract of animals. When ingested, Listeria monocytogenes commonly causes listerial gastroenteritis with symptoms of muscle pain, fever, vomiting, and diarrhea, but its more serious

[11] Are interspecies differences uncertainty or variability? The FDA routinely refers to interspecies variability but the problem equally could be thought of as uncertainty about the applicability of animal studies to humans.

form, listeriosis, can result in septisemia ("blood poisoning"), the infection of the nervous system (encephalitis and meninghitis) and, subsequently, death. Listeriosis, the object of concern, is a rare disease but more common in pregnant women, the newborn, the elderly and people with a weak immune system and it has a mortality rate of 25%. Listeria is a fairly robust organism that can survive for long periods even in refrigerators and with little oxygen, but dies at high heat and thus the most common way of eliminating it is by cooking.

In the U.S., listeria emerged as a public health concern in the 1980s when a series of outbreaks occurred. The Food Safety Inspection Service (FSIS) of the U.S. Department of Agriculture began routine testing for Listeria in 1987. Subsequently, the number of reported listeriosis cases declined but by the end of the decade the figure was on the rise again.

Listeria became an urgent concern after an outbreak in 1998-1999 that was attributed to contaminated hot dogs and deli meats. During the next three years, there were four other incidents, the two largest of those were also related to deli meats. The vast majority of the cases involved listerial gastroenteritis and only 101 resulted in listeriosis of which 21 proved fatal.

The outbreak led to one of the most thorough risk assessment documents issued by the FDA and FSIS. The first draft of the risk assessment was released in 2001 for comments. A separate 95-page technical report issued by the FSIS in May 2003 modeled the initial levels of listeria infection within meat plants. While improving the meat production process to eliminate listeria infection was a priority, the comparison of prepackaged and deli sliced meat revealed that much of the contamination happens at deli and kitchen counters as well as in the refrigerators where retailers and consumers keep the food after the meat left the factory.

The summary risk assessment document was published in September 2003 and it ran over 500 pages including appendices. An interpretative summary, itself 27 pages long, was issued separately. Following more public comments and new research, the FDA and FSIS produced an updated risk assessment on ready-to-eat (RTE) meat and poultry deli meat which was peer-reviewed in 2008 and released in March, 2009. This report complements the earlier one by including new data from a four state study in which prepackaged deli meat and deli meat sliced and packaged at retail were analyzed for listeria. Data from this report were then used as input for the models developed to capture the exposure pathways in the 2003 technical report.

In Europe, in response to a series of outbreaks, most notably a very large one in Northern Italy in 1997, a report by the Scientific Committee on Veterinary Measures relating to Public Health (SCVPH) in 1999 (SCVPH 1999) and a concurring opinion of the Scientific Committee on Food

(SCF) recommended to prescribe and enforce an upper limit of the Listeria monocytogenes in food. This critical level was determined to be 100 colony forming units per gram (cfu/g) of food. The E.U. has been monitoring listeria periodically in its member states along with other animal spread human diseases (zoonoses) such as Salmonella, Campylobacter and E. coli (EFSA 2007b, 2009a). In spite of higher awareness, the number of observed listeriosis cases in Europe increased since 2000, but now they occurred less as outbreaks, clusters of cases traceable to a common source, and more as isolated events involving mainly elderly people.

The main European risk assessment report on the problem that updated the SCVPH assessment was issued on December 6, 2007 by the Panel on Biological Hazards of EFSA (EFSA 2007c). With its 42 pages, the document is much shorter than its U.S. counterpart to which it refers to multiple times. It also draws upon another larger study conducted by The Joint FAO/WHO Expert consultation on Risk Assessment of Microbiological Hazards (JEMRA) (FAO/WHO 2004a, 2004b).

## Risk Assessment

### Process

In the U.S. two agencies were leading the risk assessment effort. The FDA and the FSIS of the USDA were working side by side with help from the Centers for Disease Control (CDC). The process involved not just peer reviews, but also a public meeting in February 2003 and the solicitation of public comments. Submissions were received from a wide variety of groups from industry, including trade associations representing the food industry, companies manufacturing food processing equipment, marketers, processors and distributors of agricultural and food products, as well as from consumer groups, expert risk assessors and modelers, and representatives of educational and scientific societies (FDA/USDA 2003a). Much of the work was done by the staff of the main institutions, but some research tasks were contracted out, mostly to research universities.

In the E.U., the first risk assessment was delivered by the SCVPH but EFSA, founded in 2002, and its Panel on Biological Hazards took over. The monitoring and data gathering was the responsibility of the member states and EFSA and the European Commission led the effort to standardize the information. There was no public consultation on the risk assessment of listeria.[12]

[12] According to EFSA's web site, there was a call in May 2008, after the listeria report was published for public comments on foodborne anti-microbial resistance. As more and more bacteria develop resistance to anti-microbial

## Content

Listeria, like most microbiological hazards has various strains with different capacity to adhere to surfaces, to survive in various environments and to cause sickness. Biohazards require a different approach from risk assessors than contaminants because all of these additional factors must be considered when the risk of a biohazard is assessed.

> "The primary variables involved in constructing dose-response models for *Listeria monocytogenes* are pathogen virulence (the ability of the pathogen to produce illness), host susceptibility (the capacity of the host to defend against the pathogen), and the effect of the food matrix (the relationship between the physico-chemical nature of *Listeria monocytogenes* contaminated food and the fate of the organism following ingestion). Because of variability in host susceptibility and food matrix effects, there is no single infectious dose for *Listeria monocytogenes*, or any other pathogen that can be used for all individuals." (FDA/USDA 2003a p.78)

In fact, this is an argument about synergy. There is no TDI calculable for listeria, because just as with synergistic chemicals, the effect of the bacteria depends on other factors. A particular characteristic of the host or the food he ate (the food matrix) may enhance (or weaken) the effect of the pathogen. Context is paramount. Listeriosis has been associated with high salt, low PH and high fat foods. These food characteristics seem to protect the bacteria and increase their virulence, just as the presence of cyanuric acid or melamide increases crystallization in the kidney (McLauchlin 1996, Dalton et al 1997).

Neither the FDA/FSIS nor EFSA produced a critical dose level, but the 100 cfu/g put forward by EFSA's predecessor, SCVPH, as the concentration level of listeria above which the probability of listeriosis increases dramatically. This value was used in the reports as the dividing line between low and high levels of contamination.

EFSA and the FDA/FSIS were both interested in estimating the size of the listeriosis threat and identifying the main culprits. To do that they had to calculate the exposure people suffer. In the more detailed description of FDA/FSIS the exposure pathway was divided into four stages: the

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agents, the public was invited to comment on this hazard. One of the bacteria was the Listeria monocytogenes. In fact, there have been only 6 calls for public consultation on biological hazards and none for contaminants. (http://www.efsa.europa.eu/en/calls.htm )

retail, the growth, the consumption and the dose-response stage. The retail stage is when the prepackaged or deli sliced meat is sold. Here the main concern is the amount of bacteria originally present in the food and the way the food becomes contaminated. Although other reports tried to model the amount of listeria infection that happens in production, both EFSA and FDA/FSIS in their reports set this question aside and started their investigation in the store, thus considering initial contamination as an exogenous variable.

The growth stage lasts from the time of purchase to the time of consumption while the meat is kept usually in the customer's kitchen mostly in the refrigerator. At this stage the focus was on the length of time and the temperature that influence the growth and virulence of the bacteria. The consumption stage is when the meat is eaten. The main issue here was exposure: the serving size and the number of servings consumed over a period. The final, dose-response stage addressed the consequences of ingesting the pathogen and, in the case of listeria, the main task is to predict the probability of death. Here along with the dosage, the food matrix, strain and susceptibility are the main variables.

Both reports concluded that decreasing contamination at retail, storing the food for a shorter time and at lower temperatures, eating less of it and less often and not being elderly or a pregnant woman or immuno-compromised, would decrease the likelihood of death by listeriosis.

Because many of these variables were poorly observed or not observed at all, a lot of guesswork had to go into the estimation. Moreover, the experts faced a daunting challenge. listeriosis is infrequent and deaths are relatively few. Mead et al (1999) estimated that not more than a total of 500 people die in the U.S. of listeriosis per year. Because the estimation looked at 23 selected ready-to-eat food categories each broken into 5 dose categories (bins) with three subpopulations modeled separately at various stages. This meant that they had to assemble the final death estimate from estimates of events with just a few expected counts.[13]

The U.S. study took great pains to spell out and quantify uncertainties and used Monte Carlo simulation to obtain plausible distributions for the calculated parameters. This technique known as quantitative uncertainty analysis (QUA) proceeded through the various stages. It established an uncertainty distribution for each parameter based on expert estimates and used the observed variability of characteristics when those were available. Instead of carrying out a set of deterministic calculations, QUA takes random values from each distribution and calculates an estimate producing a different one each time. The final result is not a single value but a distribution of estimates.

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[13] Counts are natural numbers: they are non-continuous and truncated at 0.

The part of the model covering stages one to three, intended to estimate exposure to the bacteria deployed a two-dimensional Monte Carlo model where one dimension represented the variation in the capacity of a serving of food to cause listeriosis. This estimate was based on listeria concentration at the retail store, amount of deli meats consumed per serving, microbial growth rates, storage time and temperature, strain virulence and host susceptibility. The second dimension represented uncertainty in the estimates. The second part of the model addressed the last step, dose-response. The distribution of the number of death from listeriosis was obtained with a one-dimensional Monte Carlo model representing uncertainty only (as it was based on estimates of population parameters such as total annual number of servings consumed or death rates per serving observed in mouse data).

The resulting distribution which was adjusted to be consistent with CDC estimates combined the original variability and uncertainty distributions and had a larger variation and fatter tails (i.e. indicated that extreme values are more likely) than its components reflecting cumulative uncertainty. Unsurprisingly, this cumulative uncertainty led to conclusions that were unsurprising.

> "The risk assessment ***reinforces*** past epidemiological conclusions that foodborne listeriosis is a moderately rare although severe disease. […]
> The risk assessment ***supports*** the findings of epidemiological investigations of both sporadic illness and outbreaks of listeriosis that certain foods are more likely to be vehicles for *L.monocytogenes*." [FDA/USDA 2000c 3 p. 26, emphasis added]

It also found that susceptible people are more likely to get listeriosis and that consuming more food that is infected and eating food with higher levels of listeria are more likely to result in sickness and death. The summary reiterated earlier findings about which groups are more susceptible, and reconfirmed the importance of storage time and temperature. The only piece of novelty came not from the models but from considering

> "…for the first time, the range of virulence observed among different isolates of *L. monocytogenes*. The dose-response curves suggest that the relative risk of contracting listeriosis from low dose exposures could be less than previously estimated." [p.26.]

EFSA reached the same set of conclusions, and while it did comment on various uncertainties in the analysis, unlike its U.S. counterpart, it did not feel it was necessary to go to great length to quantify uncertainty. Quantitative uncertainty analysis in the U.S. report did not rule in or rule out anything that was not already accepted before. Had it done so, it surely would have generated criticism pointing to model assumptions as arbitrary. In other words, yet another set of uncertainties (hitherto unknown unknowns) would have been invoked by the critics.[14]

Whether a particular factor is treated as a case of variability or uncertainty does not depend only on availability of information but also on the causal model the experts work with. Causation is central in policy research and even when the risk assessment aims at purely estimating a particular quantity, its models will be built on causal mechanisms.

In the listeria studies differences in individual susceptibility and strain virulence were mentioned among the factors to be treated as variation. Both susceptibility and virulence are quasi-tautological properties of people and bacteria, respectively, when treated as causes of sickness or death. Susceptible people are, by definition more likely to fall ill and virulent pathogens are, by necessity, more likely to cause that. If these factors were aleatory, they would indeed matter only by making the effect of other factors (e.g., the pathogen's concentration in a food item, serving size and frequency of consumption) less predictable thus more uncertain.

Neither susceptibility nor virulence, however, is random. About susceptibility we know that the elderly, the very young and people with compromised immune systems are the ones most susceptible (USDA/USDA 2003a p.76-7.). Strain is also non-random and we know quite a bit about the relative virulence of various Listeria monocytogenes serotypes and rybotypes and their involvement in outbreaks (Farber and Peterkin, 1991, Pinner *et al.*, 1992, Wiedman *et al.*, 1997). If we knew, for instance, that only immune-suppressed people die of listeriosis, or that only serotype 4b causes outbreaks, the fact that people with a healthy immune system don't die or that other serotypes are not virulent – i.e., there is variation in susceptibility and strain – will pose no uncertainty whatsoever. We still may not be able to predict who dies of listeriosis with perfect precision but that remaining uncertainty will be due to other factors.

Observed variation in susceptibility may be just an indication of a person's age and the strength of her immune system, two pieces of information we must obtain. By the same token, the

[14] A long list of such arbitrary assumptions are pointed out by the peer review in Appendix 2 of the report including the arbitrariness of food categorization, distributional assumptions and data selection [FDA/USDA 2003b pp. 277-324].

variability of strain virulence is a signal of our lack of knowledge of the sero- and rybotype of the bacteria. Then each is a case of epistemic uncertainty that can be remedied with more information. Where we draw the boundaries of our causal model, -- where we stop our causal chain, --therefore, decides what counts as variability and epistemic uncertainty at a given level of knowledge. The more widely we draw the circle the more uncertainty we will have.

The complexity of QUA stands in stark contrast with the simple convention based accounting for uncertainty used in the melamine case. We believe this contrast to a large extent is due to different epistemic cultures and the larger role of complex modeling in the biological hazard field which in turn is consequence of the larger role context plays in the field. Yet the markedly larger enthusiasm for complex modeling of uncertainty in the U.S. is at least partly due to the greater openness of the risk assessment process. Complex model building creates closure around core experts by excluding potential critics without the requisite technical knowledge, at the same time it provides legitimacy in an adversarial system by invoking objectivity (even though uncertainty distributions in QUA are built on informed yet still subjective judgments). The European system creates closure bureaucratically and builds legitimacy through the selection of its experts.

## Conclusion

Creating a universal approach to risk analysis and measurement of uncertainty may be desirable from the perspective of large agencies such as the U.S. Office of Management and Budget or the European Commission that must participate in managing different types of risks from natural disasters to terrorism, and need to cognitively process, compare and prioritize them, but a common methodology seems to be elusive even in the relatively narrow field of food safety. How much uncertainty is found will always depend on how the causal problem is demarcated and what unknowns are considered relevant. This, in turn, will be influenced by the conventions of the epistemic community charged with assessing the risk and the institutional arrangements that frame the process.

The effects of epistemic norms and institutional processes are not additive. The effect of institutions depends on the culture of the epistemic communities. In our case, institutional pressures to formalize uncertainty analysis seem to be smaller in chemical than in biological hazards because there is a synergism between the larger role complex modeling plays in that field and the complex modeling approach of QUA.

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