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FDA-iRISK—A Comparative Risk Assessment System for Evaluating and Ranking Food-Hazard Pairs: Case Studies on Microbial Hazards

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ABSTRACT

Stakeholders in the system of food safety, in particular federal agencies, need evidence-based, transparent, and rigorous approaches to estimate and compare the risk of foodborne illness from microbial and chemical hazards and the public health impact of interventions. FDA-iRISK (referred to here as iRISK), a Web-based quantitative risk assessment system, was developed to meet this need. The modeling tool enables users to assess, compare, and rank the risks posed by multiple food-hazard pairs at all stages of the food supply system, from primary production, through manufacturing and processing, to retail distribution and, ultimately, to the consumer. Using standard data entry templates, built-in mathematical functions, and Monte Carlo simulation techniques, iRISK integrates data and assumptions from seven components: the food, the hazard, the population of consumers, process models describing the introduction and fate of the hazard up to the point of consumption, consumption patterns, dose-response curves, and health effects. Beyond risk ranking, iRISK enables users to estimate and compare the impact of interventions and control measures on public health risk. iRISK provides estimates of the impact of proposed interventions in various ways, including changes in the mean risk of illness and burden of disease metrics, such as losses in disability-adjusted life years. Case studies for *Listeria monocytogenes* and *Salmonella* were developed to demonstrate the application of iRISK for the estimation of risks and the impact of interventions for microbial hazards. iRISK was made available to the public at http://irisk.foodrisk.org in October 2012.

All stakeholders in the system of food safety would benefit from the availability of a tool that enables rapid, transparent, and rigorous evaluation of risks from foodborne hazards. The numerous combinations of foods and hazards make risk assessment across a broad mandate extremely challenging. In particular, federal agencies require evidence-based and transparent approaches to assess, compare, and evaluate the risk of foodborne illness from microbial and chemical hazards and the public health impact of interventions. Comparative risk assessment, sometimes called risk ranking, is integral to food safety decision making *(26)*. Given the multitude of potential foodborne hazards, limited resources should be focused on the greatest risks (and ideally, the greatest opportunities for risk reduction) among the many hazards, commodities, and farm-to-table stages in the food supply system. Assessing food safety risk over the product life cycle and over a large mandate requires the integration of science and state-of-the-art information technology to identify the food-hazard combinations posing the highest risks, to explore interventions to prevent harm, and to respond immediately when contamination and illness occur.

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As further evidence of the need for comparative risk assessment tools, an expert committee convened by the National Academy of Sciences *(26)* recommended that the U.S. Food and Drug Administration (FDA) develop tools for public health risk ranking as part of the iterative steps in a risk-based system for enhancing food safety decision making. The Academy panel recommended that the FDA create a model that is fit for purpose and ''scientifically credible, balanced, easy to use, and flexible'' *(26)* to conduct public health risk ranking in a systematic manner.

The FDA Food Safety Modernization Act, enacted in 2011 *(43),* emphasized the need for risk determination, including low versus high public health risk with regard to food products, production activities, and food facilities. For example, the designation of foods as high risk through risk assessment is needed for promulgating regulations pertaining to a product tracing system. In setting standards for produce safety, assessment is required to compare differences in risk associated with fruits and vegetables that are raw agricultural commodities. Risk analysis of on-farm manufacturing, processing, packing, or holding activities is needed for exempting from mandatory preventive controls certain facilities that engage in activities determined to be low risk and involving specific foods determined to be low risk. Implicit in each of these requirements is the need to

compare risks for many foods and hazards in parallel rather than evaluating one combination at a time.

Assessing the risk associated with various hazards and products can be challenging because of the complex and global nature of the food supply. Foods can be contaminated with microbial pathogens, microbial toxins, and chemical hazards at one or more points in the food supply system. Food safety hazards may be introduced from primary production on the farm, during processing, manufacturing, and retail distribution, and during food preparation at retail establishments or in homes. Control measures and interventions can also be identified and applied at various points in the system. A comparative risk assessment tool is needed to allow a systematic analysis of data for contamination, consumption, dose-response relationships, and health effects to identify the most significant risks and risk reduction opportunities based on public health metrics.

Identifying, comparing, and in some cases prioritizing food safety risks can involve a range of qualitative, semiquantitative, and quantitative methods. Various methods and their applications have been published. Qualitative decision trees or risk rules, such as a likelihood-severity grid for qualitative risk ranking *(4),* are examples of qualitative methods. Semiquantitative risk scoring includes the pathogen-produce pair attribution risk ranking model *(1),* the Risk Ranger *(32)* for determining relative risks for different product-pathogen-processing combinations, and the Food Safety Universe Database *(6, 26)* for ranking risks from food-hazard-location combinations in the food supply.

Many examples of quantitative risk assessment models have been published, notably the FDA and the Food Safety and Inspection Service (FSIS) risk assessments of *Listeria monocytogenes* in ready-to-eat foods *(41)* and *Vibrio parahaemolyticus* in raw oysters *(38).* The FDA and FSIS *L. monocytogenes* risk assessment included the development of a complex mathematical model with inputs of available exposure data for 23 ready-to-eat food categories and three dose-response models. The model predicted relative risk rankings among the 23 food categories based on outputs for two public health metrics (cases per serving and cases per year).

Both quantitative and qualitative methods of risk ranking can be useful for informing policy decisions, depending on the problem, the time frame, the specific risk management questions to be addressed, the availability and quality of the data, and the availability of resources. A readily accessible and structured system is desirable as both a risk assessment tool and a knowledge repository to inform food safety decision making, which often takes place in real time. Here, we describe the development and application of the FDA-iRISK (referred to in this article as iRISK) system, a Web-based database and quantitative risk assessment tool for storing evidence in a structured fashion and then assessing and comparing the health impact of microbial and chemical hazards in foods. To illustrate the capacity of iRISK, we present case studies for *L. monocytogenes* and *Salmonella* from an existing FDA library, including risk estimates for multiple food-hazard combinations and the impact of interventions.

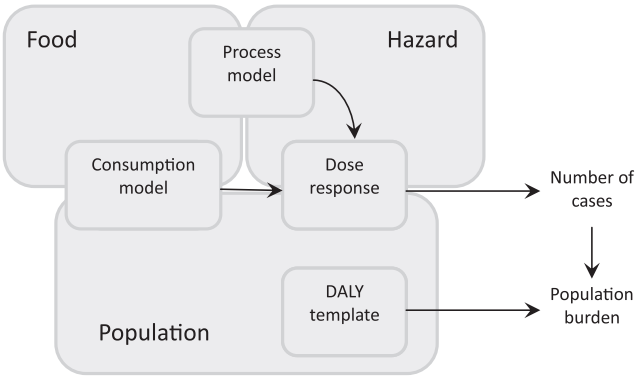

FIGURE 1. *Seven elements of a generic risk scenario in iRISK and their relationships.*

MATERIALS AND METHODS

iRISK development and peer review. The iRISK system was developed through partnership and collaboration with experts within and outside the government. iRISK originated from and built upon a risk ranking prototype developed through a cooperative agreement (grant) between the FDA and the Institute of Food Technologists (IFT). An expert panel with expertise in the food supply system, food safety, risk assessment and management, microbiology, toxicology, and other related areas was convened to develop the framework for the prototype *(29).* The FDA also commissioned a study conducted by RTI International (Durham, NC) to evaluate food safety risk ranking and prioritization models (at a later time RTI International also assisted with proof-of-concept testing of an earlier version of iRISK). Some of the models evaluated were published, but others were not available in the public domain. Based on the evaluation of the scope, strengths, and limitations of the available models, the FDA selected the IFT framework for further development. The IFT framework was operationalized into a series of quantitative risk assessment model elements by Risk Sciences International. The risk assessment model elements are combined with a relational database, a user interface, and report generation capabilities to form a Web-based program, designated iRISK. iRISK has undergone an external peer review for underlying algorithms and mathematical equations and the usability of the interactive Web interface, with a focus on microbial hazards. The FDA published a peer reviewed report describing efforts to expand the capacity of iRISK and enhance the user interface as suggested by the peer review panel *(39).*

iRISK model elements and their relationships. A risk scenario developed in iRISK is a quantitative risk assessment for a food-hazard pair to estimate the risk it poses to a population. The Web interface enables users to define the food and the hazard of interest, edit inputs, update references and assumptions, and store, view, and share data, information, and risk scenarios. Figure 1 illustrates the seven elements of a generic risk scenario: the food, the hazard, the population of consumers, a process model (i.e., food production, processing, and handling practices), consumption patterns in the population, dose-response relationships, and burden of disease measures associated with health effects (e.g., losses in disability-adjusted life years [DALYs]).

The iRISK model is consistent with the Codex risk assessment paradigm *(10, 11)*; hence, data inputs fall into two domains: exposure assessment and hazard characterization. Inputs in the exposure assessment domain focus on consumption patterns in the population, introduction of the hazard, and changes to the level and prevalence of the hazard through the farm-to-fork chain.

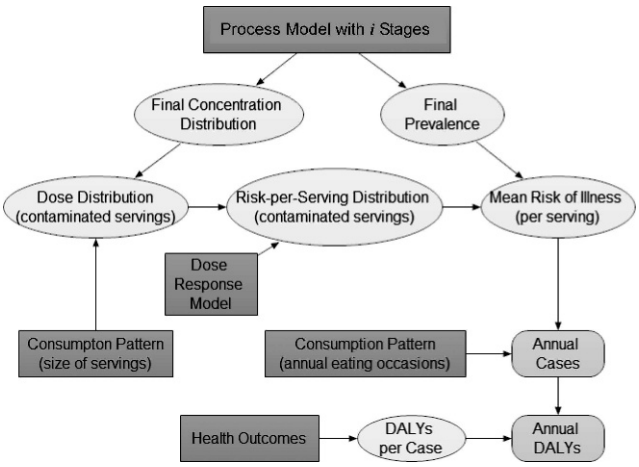

FIGURE 2. *iRISK model inputs and outputs for a food-hazard risk scenario (microbial hazards). User inputs are indicated by square nodes. Model outputs are indicated by oval nodes, with the ultimate risk output being the Annual DALYs for a food-hazard pair under evaluation. The data inputs as shown apply to a risk scenario in which the food is contaminated with a microbial hazard or a chemical hazard that causes acute effects. A risk scenario involving a chronic hazard includes the same inputs and outputs, except that consumption inputs are the amount consumed per day and the number of consumers.*

Inputs in the hazard characterization domain focus on the hazard pathogenicity or toxicity (expressed as a dose-response relationship) and the public health burden associated with infection or toxic effects of the hazard.

Structure of a generic model for microbial and chemical hazards. iRISK is designed to estimate risk associated with both microbial and chemical hazards. Figure 2 illustrates the inputs and outputs of a generic model for a food-hazard pair with a microbial hazard. This generic model also applies to a scenario in which the hazard is a chemical agent that causes an acute health effect. For a food-hazard pair in which the hazard is a chemical agent that causes chronic health effects, the overall underlying model structure is similar, but consumption patterns and doses are defined and measured differently. In this study, we focused on microbial hazards. The process model with multiple stages (Fig. 2) starts with the initial conditions of a pathogen in a food, i.e., the proportion of contaminated units (prevalence) and the distribution of the contamination in the contaminated units. The changes in contamination prevalence and levels as a result of food production, processing, and handling practices are modeled to estimate the final prevalence and concentration distribution of the hazard in contaminated units at the point of consumption. iRISK integrates the user-provided evidence inputs based on built-in templates and mathematical equations according to the biological and handling processes specified by the user. The outputs are generated by Monte Carlo simulations. The computations, including the Monte Carlo simulations, are conducted using the Analytica Decision Engine (Lumina Decision Systems, Los Gatos, CA). The mathematical architecture of iRISK has been peer reviewed *(39)*. Technical details on the models and equations employed are described in the technical documentation *(19)* available on-line with the iRISK tool.

Input elements for a food safety risk scenario. The user begins by specifying hazards, foods, and populations of interest and inputs data corresponding to the exposure assessment and hazard characterization domains. iRISK provides the model framework and templates, and the user chooses the template appropriate for a risk scenario and provides evidence (including the opportunity for providing a rationale for the selection of the evidence) for the seven elements (Fig. 1) within the framework.

Element I: foods. The definition of food affects the process model (e.g., the process model for peanut butter is different from that for soft ripened cheese). The granularity of the food classification (e.g., soft ripened cheese versus brie) depends on the specific purposes of the evaluation.

Element II: hazards. The type of hazard affects process model options (see description of process types below) and dose-response options provided within iRISK for the hazard. Risk ranking is done on the basis of the health burden for a food-hazard pair.

Element III: population groups. The choice of population group is linked to the choice of the dose-response model, specific patterns of health effects, and the consumption model. Depending on the risk scenario, one or more population groups (e.g., perinatal population or adults 60 years or older) and life stages of interest (e.g., early childhood or a duration of 5 years) can be defined.

Element IV: process models. The process model describes the impact of food production, processing, and handling on the level and prevalence of the hazard. The outputs from the process model are the probability distribution of the level of the hazard in the food at the time of consumption and the prevalence of contaminated servings; these data are used to predict ingested dose and the number of cases of illness. The data requirements for a process model include the initial conditions (i.e., initial prevalence, initial distribution of the hazard, and the unit mass), followed by process stages from farm to table (or a smaller scope) of the food supply chain up to the point of consumption.

Process models are defined as a succession of process stages, events, or steps along the farm-to-fork continuum. Each process stage is defined by a process type that describes the impact of the stage on the hazard and the unit size of the food. The process type describes what happens in an individual process stage, expressed as a fixed value or as a probability distribution representing variability. A process type may be selected from a menu of built-in process types that have been customized for this application. The process types and the associated mathematical equations describe the major process mechanisms that affect the prevalence, level, and spatial distribution of a microorganism. Mathematical equations describing the process types have been peer reviewed *(39)* and are similar to those previously published *(18, 27, 28)*. The process types and their data inputs are further described in Table 1.

Element V: consumption models. The consumption model is defined in relation to the specified population group. For microbial hazards, the distribution of the amount of food eaten (i.e., serving size) during each eating occasion and the number of eating occasions (i.e., number of servings) annually are required inputs. For chemical hazards, the distribution of the average amount of the food eaten daily (over a period of time or a lifetime) and the number of consumers are required.

Element VI: dose-response models. The dose-response relationship predicts the probability of a specific biological effect (response) at various levels of ingestion (doses) of a hazard. The

TABLE 1. *Process types and data inputs describing the impact of a process stage on microbial and/or chemical hazards*

Process type	Description of data inputs[a]
Increase by growth	This process type is applied to microbial hazards only. It describes the increase in level (a distribution or a fixed value on a log scale such as log CFU) due to growth of the bacterial pathogen, while prevalence is assumed to be unaffected.
Increase by addition	This process type represents the addition of the hazard in the amount of the specified addition to a unit of the food[b] (a distribution or a fixed value on a log scale such as log CFU or log PFU of a microbial hazard to a unit, or grams of a chemical hazard to a unit). The likelihood of such an addition occurring is also required (a fixed value from 0 to 1). This process type may be used to describe an increase in prevalence and/or concn or level as a consequence of cross-contamination, e.g., from the processing environment.
Decrease	This process type describes the removal or inactivation of some fraction of the hazard. For chemical hazards, the decrease is defined by a fixed value or a distribution that ranges from 0 (no decrease at all) to <1, because total elimination is assumed to be impossible. For microbial hazards, the decrease is defined usually by a distribution or by a fixed value of the log reduction in the level of contamination within the contaminated units. A reduction in prevalence is possible when the microbial hazard decreases because the individual microbes are discrete units. In contrast, chemical contamination is assumed to be continuous (i.e., distributed homogeneously throughout contaminated units); this process type leads to a diminution of the concn in contaminated units without change in the prevalence.
Pooling	When units of food are combined into larger units, some contaminated units may be mixed with some uncontaminated units, resulting in an increase in prevalence and a decrease in the concn or level of the hazard in each contaminated unit. Pooling reflects the simultaneous impact of cross-contamination and dilution. The input is the new unit mass (grams) of the food, and the iRISK model computes the associated changes to prevalence and concn or level of the hazard.
Partitioning	When units of food are subdivided, the result depends on the nature of the hazard. For chemical hazards, neither concn nor prevalence would be affected because the chemical is assumed to be spread sufficiently uniformly throughout the food that it would be expected to be in all partitions of the food. Microbial hazards exist as discrete units such as individual bacterial cells (at levels typically much lower than discrete molecules of chemicals) that cannot be divided among more units of food than their own number. The input is the new unit mass (grams) of the food as a fixed value, and the iRISK model computes the associated changes to prevalence and concn or level of the hazard.
Evaporation or dilution	This process type represents the proportional increase or decrease in hazard concn or level that results from varying the mass of the contaminated unit. Inputs fall between 0 and 1 for dilution and 0 and >1 for evaporation. For example, 2 would represent a doubling of the concn or level associated with a halving of the mass (such as in evaporation), and 0.25 would represent a fourfold decrease in the concn or level that results from increasing the mass by the same factor (such as in dilution).
Redistribution (partial)	This parameter describes the factor by which prevalence increases as a consequence of cross-contamination among food units; iRISK reduces the concn or level accordingly. Therefore, the input is a multiplier (≥ 1), either a distribution of values or a fixed value, to be applied to the current prevalence level. Using the number 1 implies no change in prevalence or no cross-contamination. This process type describes cross-contamination among food units but not from the processing environment.
Redistribution (total)	Selection of this process type automatically redistributes contamination evenly among all units. For chemical hazards, prevalence is set to 1.0. For microbial hazards, prevalence is set to 1.0 when there is a high enough level of organisms to redistribute to all units or is set to the maximum value possible when the level is not high enough. In both cases, the concn or level of the hazard for each unit is reduced accordingly by iRISK, keeping the total hazard load in the system (across all units) constant. No data input is needed. This process type describes cross-contamination among food units but not from the processing environment.
No change	The process does not affect prevalence, concn or level, or unit mass; no data input is needed. This designation is useful for describing the full processing system and for explicitly noting that no effect is expected at that stage. A ''placeholder'' process type is also available to be used in the initial stages of developing a process model before specific data are available.

[a] Usually the data input is defined by a distribution of values rather than a point value to represent the variability, such as in the levels of a hazard in food or in the growth, increase, and decline of a hazard in food over the product life cycle from production to consumption.

[b] A unit is a fixed quantity of food, which is key to maintaining a clear definition of prevalence because prevalence is described as the fraction of units that have one or more pathogens or any chemical contamination. Various processes in food production will change the functional unit of food because of, for example, pooling of milk from a farm tank into a bulk tank or partitioning milk from a processing plant to individual packages of milk. The change in the functional unit must be taken into account to adjust the estimates of prevalence and level or concentration of a hazard in response to these changes.

dose-response relationship is specific to the hazard type, either microbial or chemical (further broken down by acute versus chronic hazard). Dose-response relationships specific to population groups or foods can also be developed when data are available. One of the case studies (case study 2) provides population-specific dose-response models for *L. monocytogenes,* such as for the perinatal population and for adults 60 years of age or older. Currently, sufficient data are not available to develop dose-response relationships specific to the food matrix.

Element VII: health outcomes. Foodborne illness caused by a pathogen may have more than one health outcome among different individuals in the population *(2, 17, 21, 33).* For example, infection with *Salmonella* may result in mild diarrhea, severe

diarrhea requiring hospitalization, reactive arthritis, or death *(40)*. Different hazards will cause different frequencies of health outcomes, such as the proportion of illness cases resulting in hospitalization or death *(33)*. To compare the population health burden across different hazards, it is necessary to specify health endpoints of the illness in association with the hazard and translate the endpoints into a common metric. The DALY is one of several commonly used health impact metrics that integrate information on the severity and duration of illness to estimate disease burden *(2, 17, 21)*. A DALYs-per-case value (Fig. 2) is used as a measure of the averaged burden of disease per case of illness, taking into account the relative frequency of each potential health impact. Each health endpoint is defined in terms of its duration and severity, with the burden of disease being the product of these two factors. In the case of death, duration is expressed as years of life lost based on the age of the person affected, and severity is set to the maximum value of 1.0. Users can enter different health endpoints in iRISK to create a new DALY template. Through an expert elicitation *(39),* the FDA has developed DALY templates for a number of hazards.

Case study data inputs. Case study 1 is a risk scenario for *Salmonella* (nontyphoidal) in peanut butter to illustrate the use of iRISK to estimate the population health burden for a single food-hazard pair. Through the use of built-in templates, inputs were entered for the elements of the *Salmonella* in peanut butter risk scenario (Table 2). Table 2 describes the iRISK template used for the various input parameters for the process model, the process type selected, and the input data, either as a fixed value (e.g., initial prevalence and unit mass) or as a distribution (e.g., initial level and log reduction during storage). For illustration purposes, the process model for peanut butter production was simplified, starting at the end of processing and including two stages: packaging and storage before consumption. At the end of processing, some units are contaminated, and the levels of *Salmonella* in the contaminated units are assumed to decline during storage before consumption. Data from the literature were used to estimate the initial contamination and log reduction during storage through the process model. Specific data inputs for the consumption model, dose-response model, and health effects are also shown Table 2. The iRISK templates provide the capacity to enter evidence that is required for the risk scenario in a consistent fashion and to document assumptions and sources of the data and references. These templates are described in greater detail in supplemental Tables IA, IB, and IC *(19)*. Having defined the food-hazard risk scenario by entering the evidence captured in Table 2, the scenario is available in a risk scenarios library within the individual user's iRISK database. The risk scenario is then selected for computation and reporting. iRISK constructs the model based on the evidence in the database and runs a Monte Carlo simulation while checking continuously for converging statistics of the output distribution. A report is generated as a portable document format file (Adobe Systems, San Jose, CA). The report includes a summary of the model outputs and risk scenario details, including all the input data, descriptions, and references, i.e., all the data and rationale entered by the user.

The second case study consists of risk scenarios for *L. monocytogenes* in soft ripened cheese for three population groups: the perinatal population, adults 60 years of age or older (adults 60+), and the general population (intermediate age). The perinatal population is defined as fetuses and neonates from 16 weeks after fertilization to 30 days after birth, the same definition used by the FDA and FSIS in the 2003 *L. monocytogenes* risk assessment *(41)*. Data and information inputs were the same for the hazard, the food, and the process model, whereas the three population groups were defined and the inputs were different for the dose-response model, consumption model, and DALY templates (Table 2). A more detailed description of the data, references, and rationale is provided in supplemental Tables IIA, IIB, and IIC *(19)*. The risk scenarios for the three population groups have different consumption patterns, dose-response relationships, and health effects. The model inputs for case studies 1 and 2 illustrate that although the food, hazard, and population of interest are different for the *Salmonella* risk scenario and the *L. monocytogenes* risk scenarios, the underlying model structure (Fig. 2) and the nature of the evidence required as inputs (Table 2) are the same for both pathogens. Case studies 3 and 4 included the evidence from case studies 1 and 2 to rank risks from multiple food-hazard pairs and to evaluate the effectiveness of interventions. Additional data were obtained from published studies *(23, 24, 30, 31)* and from an ongoing market basket survey to develop case study 3 on a risk scenario for *L. monocytogenes* in cantaloupes for adults 60+. The data inputs are shown in supplemental Tables IIIA, IIIB, and IIIC *(19)*.

Integration of model inputs through Monte Carlo simulations to estimate population health burden. The evidence entered for the seven elements of a risk scenario determine the level of exposure and the health impact of that exposure (Fig. 2). A risk-per-serving distribution (among contaminated servings) is generated taking into account the variability in the final distribution of the contamination (process model), the serving size distribution (consumption model), and the dose-response relationship (dose-response model). The mean risk of illness per contaminated serving is calculated from the distribution of risk (describing variability derived from any of the probabilistic inputs) generated through Monte Carlo simulation. The mean risk of illness per serving is the product of this mean and the prevalence of contaminated units at the time of consumption. The expected annual number of illness cases is calculated by multiplying the mean risk of illness per serving by the number of servings per year. The annual DALYs are calculated by multiplying the annual number of cases by the DALYs-per-case value. The iRISK Monte Carlo simulation is designed to address variability, and uncertainty can be explored by scenario analysis (e.g., changing parameters or changing distributions and comparing results).

The final result is the annual health burden, measured in DALYs lost per year, expected to result from the food-hazard combination given the assumptions for contamination, dose-response, health effects, and consumption pattern in the population in each scenario. Integration of data and information on duration and severity allow the comparison of different microbial pathogens associated with qualitatively different illness symptoms, severities, and health outcomes, including variations in the case complication (e.g., case fatality) rates among pathogens.

RESULTS AND DISCUSSION

iRISK 1.0 was used to develop the case studies reported here. These case studies are provided exclusively for illustrative purposes. The actual implementations of several of the case studies are available to users in the publicly released version of iRISK *(19)*.

Case study 1: a single food-hazard pair in one population group. The model results (Table 3) include final pathogen level (the mean of the distribution is reported), final prevalence, total illnesses, mean risk of

TABLE 2. *Examples of model inputs for food-hazard scenarios in iRISK*

Element of risk scenario	*Salmonella* in peanut butter, total population			*L. monocytogenes* in soft ripened cheese, three population groups		
	Input parameter, iRISK template	Model input	Reference(s)[a]	Input parameter, iRISK template	Model input	Reference(s)[a]
Food	Peanut butter	Description	*42*	Soft ripened cheese	Description	*41*
Hazard	*Salmonella*	Description	*34, 40*	*L. monocytogenes*	Description	*41*
Process model	Initial prevalence (manufacturing)	5.50E−06	*7–9, 36*	Initial prevalence (retail)	0.0104	*15*
	Initial concn	Uniform (−1.52, 2.55) log CFU/g	*5, 22, 34, 44*	Initial concn	Triangular (−1.39, −1.15, 0.699) log CFU/g	*15*
	Initial unit mass	6.85E+06 g		Initial unit mass	227 g	*15*
	Process stage 1: packaging, partitioning	Unit mass 250 g		Process stage 1: consumer storage, increase[b]	Triangular (0, 0.03, 5.79) (log CFU)	*12, 41*
	Process stage 2: storage, decrease	Uniform (0.49, 3.47) log CFU	*5*	NA		
Consumption model	Grams per eating occasion	30 g	*20, 37*	Grams per eating occasion[c]	(i) Triangular (10, 28, 85); (ii) Triangular (10, 28, 85); (iii) Triangular (10, 28, 168)	*41*
	Eating occasions per year	1.7E+10		Eating occasions per year[c]	(i) 1.2E+07; (ii) 1.8E+08; (iii) 1.7E+09	*41*
Dose-response model	Beta-Poisson model	$\alpha = 0.1324$; $\beta = 51.45$	*13*	Exponential[c]	(i) 4.51E−11; (ii) 8.39E−12; (iii) 5.34E−14	*14*
Health effects	DALY template (salmonellosis general population)	0.019 DALYs per case	*2, 33, 40*	DALY templates (listeriosis)[c]	(i) 14 DALYs per case; (ii) 2.6 DALYs per case; (iii) 5.0 DALYs per case	*21, 25*

[a] Detail description of rationale can be found in the supplemental Tables IA, IB, IC, IIA, IIB, and IIC *(19),* including assumptions made in using data and information from the listed references to derive the model inputs for the risk scenarios.

[b] The ComBase Predictor (http://www.combase.cc) was used to determine growth based on times and temperatures during consumer storage. See details in supplemental Table IIB *(19).*

[c] Inputs are defined separately for consumption, dose-response, and health effects for the three *L. monocytogenes* risk scenarios: (i) the perinatal population, (ii) adults 60 years of age and older, and (iii) the intermediate-age population (5 to 59 years of age). The three risk scenarios have the same food, hazard, and process model.

TABLE 3. *iRISK output example: summary results for a single food-hazard pair*

Scenario	Final mean level (log CFU/g)	Final prevalence	Total no. of illnesses	Mean risk of illness	No. of eating occasions	Annual DALYs	DALYs per eating occasion
Salmonella in peanut butter, total population	0.273	4.18E−06	3,380	1.99E−07	1.70E+10	63.5	3.74E−9

illness, total eating occasions, annual DALYs, and DALYs per eating occasion. The detailed report generated for each scenario contributes to the documentation, knowledge base development, transparency, and consistency that is key to the application of comparative risk assessment.

The mean risk of illness is the average probability of illness from one serving or eating occasion and was generated through Monte Carlo simulations from the mean of the risk-per-serving distribution among contaminated servings (an intermediate result not shown) and the final prevalence of contamination in the food. The results shown in Table 3 accounted for variability of all inputs for a food-hazard pair. When the final prevalence of the pathogen contamination in food is low (e.g., less than 1%), as is often the case, the majority (e.g., >99%) of the servings are not contaminated. The risk per serving for these noncontaminated servings is 0. The 5th, 95th, and 99th percentiles of the risk per serving (among all servings) is then 0. The mean risk of illness per serving (among all servings) will likely also be very low; nevertheless, it is not 0 because the risk for the <1% of contaminated products is not 0. This was the case for the risk scenario *Salmonella* in peanut butter (Table 3), where the final prevalence was approximately 4E−6 (approximately 4 in 1 million) and the mean risk of illness per serving was approximately 2E−7 (or 2 cases per 10 million servings). The Monte Carlo approach applied in iRISK, which focuses computation resources on only contaminated units, is much more efficient than simulation of both contaminated and noncontaminated units, given the low prevalence expected in the final servings for many food-hazard pairs.

Case study 2: a single food-hazard pair in three population groups. Based on the data inputs for *L. monocytogenes* in soft ripened cheese and the population groups, iRISK generated risk estimates through Monte Carlo simulations for each of the three risk scenarios (Table 4). The mean risk of illness was 7.1E−8 for the perinatal population, 1.3E−8 for adults 60+, and 1.4E−10 for the intermediate-age population. The difference was primarily driven by the difference in the assumed *L. monocytogenes* dose-response relationship among the three population groups (Table 2), given that the same process model was used, which resulted in the same final mean level and the same final prevalence of *L. monocytogenes* in the soft ripened cheese at the point of consumption. Combining the mean risk of illness output with the number of servings per year, the expected annual number of cases was determined (results not shown) and subsequently translated into annual DALYs loss of 11.7, 6.12, and 1.20 for the perinatal, adults 60+, and intermediate-age populations, respectively. The health metric (e.g., annual DALYs lost) formed the basis for risk ranking for multiple risk scenarios.

iRISK was further employed to characterize uncertainty about the annual DALYs, using the intermediate-age population as an example. The uncertainty analysis for the predicted annual DALYs was obtained through sensitivity analysis focused on the dose-response relationship. The inputs for the dose-response model were different r values (the single parameter of an exponential dose-response model) representing the 5th percentile (r = 1.42E−14), median (r = 5.34E−14), and 95th percentile (r = 1.02E−13) of the r value uncertainty distribution from the Food and Agriculture Organization of the United Nations and the World Health Organization *(14)*. The resulted annual DALYs were 0.320 (5th percentile), 1.20 (median), and 2.30 (95th percentile) for the uncertainty estimates. The median DALYs result was used in risk ranking.

Case study 3: risk ranking for multiple food-hazard pairs. From the FDA iRISK library, we selected five risk scenarios for ranking, including the food-hazard pairs developed in case studies 1 and 2 and a risk scenario for *L. monocytogenes* in cantaloupes for adults 60+. The case studies illustrate that iRISK allows risk ranking of population health burden across many different dimensions: multiple population groups (Table 4), multiple foods (Table 5), and multiple food-hazard combinations (Table 6). Table 4 shows risk ranking among three population groups: *L. monocytogenes* in soft ripened cheese for the perinatal population, intermediate-age population, and adults 60+. Table 5 shows an example of risk ranking for two different foods, soft ripened cheese and cantaloupe, for the same populations in a baseline nonoutbreak situation. All five risk scenarios can be

TABLE 4. *iRISK output example: risk ranking across multiple population groups*

Scenario of *L. monocytogenes* in soft ripened cheese	Final mean level (log CFU/g)	Final prevalence	Total no. of illnesses	Mean risk of illness	No. of eating occasions	Annual DALYs	DALYs per eating occasion
Perinatal population	3.55	0.0104	0.850	7.08E−8	1.20E+07	11.7	9.77E−7
Adults 60 yr and older	3.55	0.0104	2.37	1.32E−8	1.80E+08	6.12	3.40E−8
Intermediate-age population	3.55	0.0104	0.242	1.42E−10	1.70E+09	1.20	7.08E−10

TABLE 5. *iRISK output example: risk ranking across multiple foods*

Scenario of *L. monocytogenes* in adults 60+	Final mean level (log CFU/g)	Final prevalence	Total no. of illnesses	Mean risk of illness	No. of eating occasions	Annual DALYs	DALYs per eating occasion
Cantaloupe	2.32	0.0130	2.39	2.22E−9	1.08E+9	6.18	5.72E−9
Soft ripened cheese	3.55	0.0104	2.37	1.32E−8	1.80E+08	6.12	3.40E−8

selected for ranking (Table 6), although the food-hazard pairs are being compared for different population groups. In some cases, it may be important and more informative to make comparisons based on the same population. The health burden associated with *L. monocytogenes* in soft ripened cheese for the total U.S. population is the sum of that from the perinatal and intermediate-age populations and adults 60+. We used a risk scenario grouping option in iRISK to aggregate the total DALYs from the three population groups and compared the aggregate DALYs for *L. monocytogenes* with the annual DALYs for *Salmonella* in peanut butter in the total U.S. population (Table 6). These examples illustrate the flexibility of the iRISK system, which can be used to address different questions to meet different risk management decision-support needs.

Case study 4: evaluation of interventions. The predictive multistage process model is the means by which iRISK enables evaluation of control measures and potential interventions. For case study 2, the baseline risk scenario for *L. monocytogenes* in soft ripened cheese for the perinatal population included the amount of growth as having a Triangular probability distribution (minimum = 0, mode = 0.03, maximum = 5.79), with units of log CFU. The maximum growth of 5.79 log CFU was based on the assumption of 15 days of storage at 13.0°C (see supplemental Table IIB *(19)*). We conducted sensitivity analyses using iRISK to evaluate the impact of reduced storage temperature through interventions such as consumer education. When the maximum storage temperature is reduced from 13.0°C (supplemental Table IIB, mean temperature + 4 SD) to 10.6°C (mean + 3 SD) or 8.2°C (mean + 2 SD), the growth of *L. monocytogenes* (maximum level) during consumer storage would be reduced from 5.79 to 3.42 and 1.64 log CFU, respectively. The corresponding predicted annual loss in DALYs would decrease from 11.7 to 0.128 and 0.00817, respectively, keeping all other inputs in the model unchanged.

iRISK can be used to evaluate interventions at any of the stages in the process model. Using the *Salmonella* in peanut butter risk scenario, we evaluated the impact of interventions in the processing environment on predicted health burden in the total population. For example, food producers may implement measures such as controlling personnel and material movements, applying hygienic equipment design principles, and minimizing or eliminating moisture in the peanut postroasting area *(16)* to reduce the levels of *Salmonella* contamination in the postroasting stages of production. If such control measures decrease contamination from the baseline (uniformly distributed on the log scale between 1.52 and 2.55) for the initial level by reducing the maximum level by 1 or 2 log CFU, the predicted annual loss in DALYs would be reduced by 67 and 93%, respectively (Fig. 3).

The results presented in these case studies were based on the data inputs and assumptions made; the predicted mean risk of illness and annual DALYs will change as different inputs are used. The risk scenarios, risk estimates, and risk rankings presented in this study are primarily for illustration purposes. Because the data are stored in each user's unique registry within iRISK, the risk scenarios can be easily retrieved and updated with new data and updated assumptions.

Future considerations. Ongoing efforts are being made to further improve and validate the iRISK model, including further testing, adding functionalities such as more probability distribution options, and improving the capacity of iRISK to predict health burden of microbial toxins. iRISK is flexible; in addition to the DALY metric, other health impact metrics such as cost of illness *(3, 35)* may be added to the system. Ongoing efforts include increasing the library of food-hazard pairs. Like any quantitative risk assessment, development of a risk scenario in iRISK is data intensive. Data are needed from multiple sources, including the scientific literature, government

TABLE 6. *iRISK output example: risk ranking of population health burden across multiple hazards, foods, and population groups*

Scenario	Final mean level (log CFU/g)	Final prevalence	Total no. of illnesses	Mean risk of illness	No. of eating occasions	Annual DALYs	DALYs per eating occasion
Group 1: *Salmonella* in peanut butter, total population	0.273	4.18E−06	3,380	1.99E−07	1.70E+10	63.5	3.74E−9
Group 2: *L. monocytogenes* in soft ripened cheeses							
Total population						19.0	
Perinatal population	3.55	0.0104	0.850	7.08E−8	1.20E+07	11.7	9.77E−7
Adults 60 yr and older	3.55	0.0104	2.37	1.32E−8	1.80E+08	6.12	3.40E−8
Intermediate age population	3.55	0.0104	0.242	1.42E−10	1.70E+09	1.20	7.08E−10

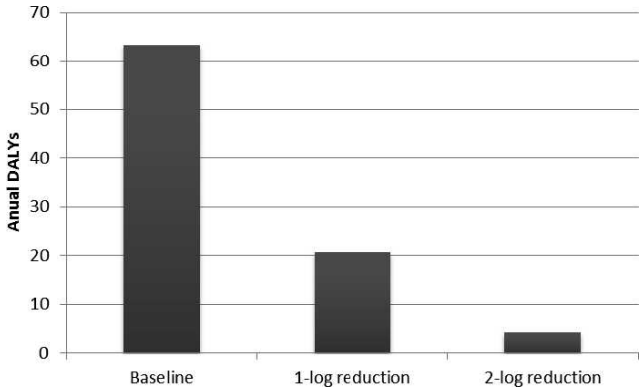

FIGURE 3. *iRISK output example: evaluation of intervention for the* Salmonella *in peanut butter risk scenario. Assuming improved control measures in the processing environment that reduces the maximum level of* Salmonella *contamination postroasting, the impact of the intervention on the annual DALYs was conducted using sensitivity analysis in iRISK. The inputs for the scenarios for the baseline and 1-log and 2-log reductions in the maximum level were distributions Uniform (−1.52, 2.55), Uniform (−1.52, 1.55), and Uniform (−1.52, 0.55), respectively.*

surveys (e.g., the National Health and Nutrition Examination Survey for consumption), publicly accessible databases (e.g., ComBase), expert elicitation and judgment (e.g., DALY-per-case estimates), and regulatory sampling and commissioned studies, as was shown in the case studies. Targeted data collection of prevalence and enumeration data for specific hazards in specific commodities at specific points throughout the food supply chain would help expand the library of food-hazard pairs. iRISK can be used to understand what takes place in a normal baseline situation and to explore an outbreak situation.

In conclusion, iRISK is an interactive, Web-based system that enables rapid, structured, quantitative risk assessment and serves as a knowledge repository due to the underlying relational database and reporting capability. iRISK has been designed to provide breadth and flexibility of calculations and computational features to simultaneously analyze data and estimate health burden in a manner that allows comparison across many dimensions with regard to hazards, foods and food commodities, food production, processing, and handling practices, and populations and the evaluation of interventions. iRISK calculates, through Monte Carlo simulation, the number of illness cases expected based on the contamination of the food by the hazard in question, the typical consumption pattern, and the dose-response relationship and then translates the number of cases into a public health metric to permit comparison of the public health burden across multiple food-hazard pairs. The FDA anticipates further enhancing the capacity and expanding the application of iRISK to support decision making to ensure food safety. iRISK version 1.0 was made available to the public in October 2012 *(19)*.

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