Food Research International 64 (2014) 371–379

Contents lists available at ScienceDirect

Food Research International

journal homepage: www.elsevier.com/locate/foodres

Expanded Fermi Solution to estimate health risks or benefits from interacting factors

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ARTICLE INFO

Article history:
Received 30 March 2014
Accepted 3 July 2014
Available online 11 July 2014

Keywords:
Risk assessment
Nutrition
Microbial food safety
Expanded Fermi Solution
Monte Carlo simulations
Dose response curves

ABSTRACT

Food related health risk/benefit factors might be additive or multiplicative, but some can be interrelated in ways that are neither or both. Since there is always inherent uncertainty concerning the magnitude of risk/benefit factors their contribution is better represented by a probable range than a single numerical value. With the Expanded Fermi Solution method, random values of the factors are generated within their respective ranges and used to calculate the combined risk or benefit based on the chosen mathematical model. In the case of additive or multiplicative independent factors, the combined risks/benefits so calculated have approximately normal or lognormal distribution, respectively, as anticipated from the Central Limit Theorem. The distribution's mode, i.e., the most frequent value, is considered the risk's best estimate. In interactive factors, the emergence of a specific parametric distribution is not guaranteed, but the histogram of the randomly generated combined risks or benefits can be used to identify the best estimate. This is demonstrated with three abstract interactive risk/benefit models of increasing number of parameters and complexity, whose calculation has been automated and posted on the Internet as freely downloadable interactive Wolfram Demonstration. Also given is a hypothetical but realistic example of dose–response based microbial risk assessment where uncertain bacterial growth parameters are involved, which can be implemented with a new Wolfram Demonstration. The methodology and software allow rapid examination of numerous combinations of interactive factors and evaluation of their potential effect on a food's or supplement's risk or benefit.

1. Introduction

A major effort in food science and nutritional research today is directed towards the identification of the health benefits or risks associated with foods or their specific components, and explaining their physiological activity or therapeutic power. The studies are frequently initiated by discovery of a statistical relationship between diet or eating habits and health improvement or deterioration, followed by focused investigation using in vitro model systems and/or animals, and eventually humans. Translating the results of such studies into an individual's actual risk or benefit is usually hampered by the fact that numerous factors are involved, many of which are unknown or hard to quantify. Examples of unknown factors are hereditary and past or present low-level exposure to potential protagonists or antagonists. Examples of hard to quantify factors are inherent variability among individual humans in the daily amount and composition of foods consumed, the manner in which the foods are prepared and how they are consumed, e.g., with or without alcohol. All these introduce a degree of uncertainty that only increases when the exact mode of the various factors' interactions is also not fully known or is hard to assess. This is especially the case where behavioral (e.g., smoking), or occupational factors (e.g., working in a chemical plant vs. in a suburban office) also play a role. The inherent uncertainties concerning food related risks and benefits have been dealt with in different ways. The most common and intuitively obvious is the recommendation of a general minimal level for consumption or maximal level for avoidance, the basis of the official Recommended Daily Allowance (RDA). Another is to seek individual assessment given by a professional based on medical examination and available statistical data. The widely used tables and formulas produced by the Framingham Project (Sheridan, Pignone, & Murlow, 2003, Harle, Downs & Padman, 2012) serve as a good example but more restrictive studies are also used (e.g., Hu et al., 1999, Tucker, Mahnken, Wilson, Jacques, & Selhub, 1996, Mokdad, Ford, Bowman, Dietz, Vinicor & Bales, 2001, Rius, Perez, Martinez, Barez, Schiaffino & Gisperd, 2004, Holder, Scuffham, Hilton, Muspratt, Ng & Whieford, 2011.). Similar issues arise in foods' microbial safety and toxicity. Although the factors that affect them are mostly known, the magnitude of their contributions can only be estimated (see Cassin, Paoli, & Lammerding, 1998; Cassin, Lammerding, Todd, Ross, & McColl, 1998).

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http://dx.doi.org/10.1016/j.foodres.2014.07.001
0963-9969/

In a previous study (Peleg, Normand & Corradini, 2012) we proposed to deal with uncertainties concerning the factor's role, be they inherent or the result of incomplete information, by replacing the factors' assumed numerical values with their probable *ranges*. Once the main risk and benefit factors have been identified, and their probable ranges specified, Monte Carlo simulations using random values within these ranges can reveal the most likely combined risk or benefit. The procedure, which we have dubbed the 'Expanded Fermi Solution', has been automated and posted as a freely downloadable interactive Wolfram Demonstration (http://demonstrations.wolfram.com/AdditiveAndMultiplicativeRisks/). As had been expected from the Central Limit Theorem (CLT), the above-mentioned and several related Demonstrations show that when the factors' effects are additive the resulting generated combined risks have approximately normal distribution. The normal distribution's mode, i.e., the peak's location, which is the same as the mean, is in our case considered the best estimate of the combined risk or benefit — see Fig. 1 (left). Where the factors' effects are multiplicative, the generated estimates' distribution is approximately lognormal, i.e., having a rightward skew. In this case, the lognormal distribution's mode, which is smaller than the mean, is considered the best estimate of the combined risk or benefit — see Fig. 1 (right). It has also been shown that the Expanded Fermi Solution method is fairly robust against minor perturbations, i.e., minor variations in the assigned ranges do not cause major differences in the calculated best estimate of the risk or benefit (e.g., Peleg, Normand, Horowitz, & Corradini, 2007). In both the additive and multiplicative models, the risk and benefit factors are assumed to be independent. In other words, the influence of each factor on the combined risk or benefit is unaffected by that of the other factors. Theoretically at least, one can think of interactions between the factors that are not purely additive or multiplicative. For example, a particular risk can be proportional to a factor raised to a power where the power as well as the proportionality constant is a risk factor. The same could happen with a combination of nutritional benefits where one factor enhances or inhibits the influence of another in a manner that is neither additive nor multiplicative. An illustration of the difference between a purely additive or multiplicative model and 'interactive' combination model is given in Fig. 2. Obviously, the mathematical models to calculate the combined risk of purely additive or multiplicative factors would be inapplicable to an interactive combination of the kind shown at the bottom of the figure. While the previously developed formulas to estimate the combined risk would have to be modified for use in interactive scenarios, the methodology and calculation procedure could still be used. The same applies to other factor combinations that may include exponential, logarithmic or other algebraic terms.

The objective of this communication is to present the potential use of the Expanded Fermi Solution in risk or benefit assessment where the associated factors need not be merely additive or multiplicative, and to demonstrate the methodology's application in software posted as freeware on the Internet using selected hypothetical scenarios. The work is a supplement to a recent study that only addressed additive and multiplicative risks (Peleg, Normand, & Corradini, 2012) and its focus is on the mathematical procedure and its implementation. Therefore, the actual physiological, biological or other aspects of what makes foods risky or beneficial, and how the magnitude of the risk or benefit is defined and measured will not be discussed, except in the last example.

2. Mixed additive and multiplicative models and interactive factors

Consider a hypothetical oversimplified scenario where the particular combined risk, Y, is a function of only three factors r_0, f_1 and f_2 whose relationship is described by the mixed additive/multiplicative model:

$$Y = r_0 + f_1 f_2. \tag{1}$$

According to this model, r_0 is the absolute 'base line risk' determined by the individual's or group's age and gender, for example, f_1 is an added food related risk factor, e.g., excessive consumption of salt and saturated fats, and f_2 a modifier. Where $f_2 > 1$, the risk is aggravated as in the case of a person who smokes. Where $f_2 < 1$ the risk is mitigated, by routine exercises, for example. The opposite is when the factor f_1 reduces the risk, e.g., as when the person consumes plenty of what's considered healthy foods, in which case the model will be:

$$Y = r_0 - f_1 f_2. \tag{2}$$

Here $f_2 > 1$ means augmentation of the diet's beneficial effect, and $f_2 < 1$ its reduction.

The factors f_1 and f_2 can be assigned different roles and any value as long as the model will not lead to absurd consequences such as a negative risk. In a more elaborate model, the $f_1 f_2$ on the right side of the equation can be replaced by a power term, for example:

$$Y = r_0 \pm {f_1}^{f_2} \tag{3}$$

or

$$Y = (r_0 \pm f_1)^{f_2} \tag{4}$$

or

$$Y = r_0 {f_1}^{f_2} \tag{5}$$

where in all three cases the modifier f_2 would have a value close to one ($f_1 \sim 1$). Here too, $f_2 > 1$ represents raising the impact and $f_2 < 1$ lowering it.

Again, the factors' magnitudes should be restricted to values that will not result in absurd consequences, but in addition they must be in a range that will not result in a prohibited mathematical operation or complex number solution.

Suppose that for a particular individual or risk group, an expert or a group of experts, on the basis of personal knowledge or published

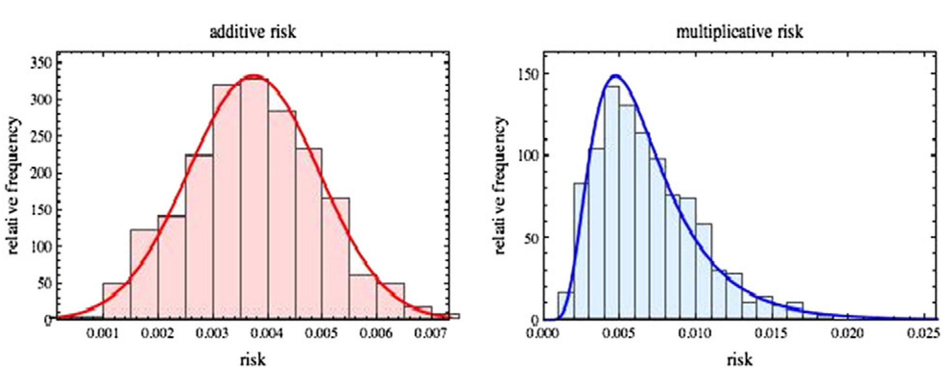

Fig. 1. The histograms of combined additive and multiplicative risk/benefit factors generated in Monte Carlo simulations. Superimposed on the histograms are the normal distribution (left) and lognormal distribution (right) having the same mean and standard deviation, or logarithmic mean and standard deviation, as the data.