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THEORETICAL PAPER

Nutrient risk assessment in a decision theoretic context

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Abstract
Background. This study describes a decision-theoretic approach to nutrient assessment based on Bayesian methods, which can be used to give accurate estimates of optimum intakes. Analysis of risk is an incomplete technique for dealing with nutrients and other substances that, by definition, have an associated benefit.
Results. This paper shows that the risk analysis methods being developed by the Codex Commission on Nutrition and European Food Safety Authority, among others, are inappropriate for assessing safe nutrient intake levels. Decision theoretic methods incorporate benefits associated with these essential nutrients, as well as potential risk. *Conclusion*. These methods allow for missing or incomplete data, which conventional risk analysis does not.

Key words: *Risk analysis, nutrient safety, decision theory, codex, 2000 Mathematics Subject Classifications 62C10, 91B16*

Introduction

Current concerns in drug evaluation and assessment have led to proposals for an update to the traditional Neyman-Pearson statistical approach to clinical trials [1]. Ten per cent of the medical devices that the Center for Devices and Radiological Health of the US Food And Drug Administration has recently approved were based on Bayesian designs and analyses, compared with none 10 years ago. New drugs are beginning to be introduced based on Bayesian analysis of experimental data [2,3].

Government dietary recommendations have been based on the subjective assessments of expert committees. This preliminary descriptive paper proposes that assessments for dietary recommendation and upper limits can be more appropriately made using a decision theoretic approach. The Bayesian approach we suggest is more closely analogous to the scientific method than the frequentist approach based on risk analysis suggested by the Codex Commission and others [4].

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Risk analysis

Current proposals for nutrient intake recommendations, such as those of the Codex Commission on Nutrition and European Food Safety Authority, are based on risk analysis. The aim is to introduce greater scientific rigour into such assessment. Any nutrient taken to excess will, at least in theory, cause toxicity. The essential nutrient water, for example, can be fatal for humans if too large a volume is taken in a single sitting [5]. For this reason, it may be necessary to assign limits as to what consumption can be considered 'safe'.

Risk analysis is a form of probabilistic risk assessment used to evaluate risks associated with an activity or action systematically. Used alone this is inappropriate for dealing with nutrition, which has an associated benefit. In risk analysis terms, nutrients carry a risk of deficit as well as a risk of excess. Risk is a measure of an event's detrimental outcome. It is concerned both with the probability of the event and the associated damage or loss. Risk analysis is a process consisting of three components: risk assessment, risk management and risk communication [6].

Risk and toxicity

Standard methods exist for the analysis of toxicity of chemicals not normally part of the diet. The reference dose (RfD) is the maximum daily exposure to a chemical, such as a pesticide, that is judged to be without risk of adverse systemic health effects over a person's lifetime. It was formerly called the Acceptable Daily Intake. The RfD has been suggested [7] to be the lower (more restrictive) value of:

- The daily dose that is expected (with 95% confidence) to produce less than 1/100 000 incidence over background of a minimally adverse response in a standard general population of mixed ages and genders,
- The daily dose that is expected (with 95% confidence) to produce less than a 1/1000 incidence over background of a minimally adverse response in a definable sensitive sub-population.

Parameters often derived from the observed toxicity include:

- The No Observable Adverse Effect Level (NOAEL) relates to the highest dose with zero measured toxicity. Note that this measure only coincides with the No Observable Effect Level for pure poisons.
- The Potency is the range of doses that produces increasing responses.
- The Maximal Efficacy is the maximal response for any dose of a given substance.
- The Lethal Dose 50% (LD50) is the dose at which half the animals die.
- The Effective Dose 50% (ED50) is the dose required to produce a specified effect in half the animals.
- The Toxic Dose 50% (TD50) is the dose at which half the animals receive a toxic effect.

Appropriate applications

Classical risk analysis is used by the US Environmental Protection Agency to decide what levels of air pollutants, such as lead, sulphur dioxide, nitrogen oxides, particulates, carbon monoxide and tropospheric ozone, are considered dangerous to the population at large [8]. From a public-health viewpoint (and ignoring any possible economic benefits of higher

levels of pollutants) this is an appropriate use of these techniques. There is no level at which the inhalation of lead-based molecules or carbon monoxide is considered beneficial.

Risk analysis is inappropriate for nutrition

Classical risk analysis, while being appropriate for environmental toxins, does not apply to optimal intakes of nutrients as it ignores beneficial effects. Risk analysis, if applied consistently, could lead for example to a recommendation that all food should be eliminated from the diet, as even small amounts of food can lead to the possibility of choking or allergic reactions. Clearly, in such a situation the benefits as well as the risks must be taken into account—avoiding food in case you choke is a far from optimal solution.

Government regulatory organizations currently ignore crucial aspects of the analysis issues such as prevalence of disease. It is often not appropriate to apply the same standards of statistical significance level (e.g. $p<0.05$) across a range of population sizes from an experiment with 20 subjects to a population of 300 million. In the latter case 15 million people would be excluded by the analysis—the 0.05 significance level would represent 15 million people in the larger group.

Nutrients are expected to have an associated benefit, unlike random chemicals, pesticides, ionizing radiation and environmental poisons. The concept of nutritional benefit has only arisen within the Codex in 2006 and then only in relation to the consumption of fish [9,10], indicating the use of an inappropriate approach essentially based on perceived risk alone. However, the necessity for a complete cost benefit analysis is clear: for example a small percentage of people are sensitive to strawberries and can have an anaphylactic response to even a slight exposure. This danger does not necessarily mean that all strawberries and foodstuffs containing the fruit or its extracts should be banned. This large effect occurs in a small minority while the majority are able to enjoy the minor benefits of the fruit.

Risk is a necessary but not a sufficient criterion for legislation. Classical risk analysis deals with the probability of harm so in the case of a complicating effect of benefits, such as with nutritional supplements, it is not expected to produce an optimal decision theoretic solution. Risk analysis, for example, provides the nutrient intake with the minimum risk of excess but, if benefits are excluded, it does not provide an optimal solution to the general decision-making problem.

Nutrition and benefit

By definition a nutrient has a positive pharmacological function. Evidence from epidemiology needs to fulfil Hill's [11] criteria as a minimum requirement for nutrient risk assessment:

- The measured correlations have to be biologically plausible. There must be a biological explanation for the phenomenon.
- The observed relationship, or correlation, must be strong. Weak relationships are simply feeble evidence.
- The effect should increase with the intake or dose. The more exposure to the substance the greater should the measured effect be.
- The relationship should be consistent. That is, results showing the absence of the effect refute the suggestion.

- The relationship should be consistent with time. If the consumption of a substance varies over the years so should the associated disease.
- The relationship should be shown independently by experiment.[1]

In particular, the concept of risk without benefit fails the first of Hill's criteria on biological plausibility. An essential nutrient is a special case as it cannot be synthesized by the organism and its absence from the diet will have a deleterious effect on the organism. Here we use the term pharmacological in its broadest sense to encompass biochemical, physiological, chemical and physical effects the nutrient causes in the organism. In this case, we have established that at zero intake the benefit is zero or negative.

Benefits and toxicity can be perceived differently depending on the frame of reference of the observer. Dietary fibre is commonly recommended for bowel health but a similar recommendation could be made with respect to other nutrients. A 5-gram dose of ascorbate will induce loose stools as a 'side effect' in some people but for others provides relief from constipation. Similarly, a dose of magnesium as magnesium oxide is taken by many to keep them regular; however in a different formulation, say magnesium citrate or chloride, more is absorbed and the effect on the bowel requires a larger dose. The benefits of nutrients and their toxicity are formulation-dependent and cannot be considered generically; for example the pharmacology of methylselenocysteine differs markedly from sodium selenite.

Analysis of nutrient risk in isolation from evidence for potential positive effects will skew recommendations towards inappropriately low doses. Benefits, like other pharmacological effects, are normally dose-related. In the absence of other data, the normal form of the log-dose response curve may be taken as a first estimate [12]. To return to vitamin C, the risk of a 2-gram dose of vitamin C may be determined to be the upper limit for daily intake based on a proportion of subjects getting loose stools. However, a proportion of people will be constipated at lower doses and might see this effect as a benefit. Moreover, the decision-making committees currently ignore additional benefits for doses far in excess of this limit. When dealing with nutrients, therefore, a more complete analytical method is required.

Decision theory

The term *decision theory* was coined in 1950 by Lehman [13] for a branch of cybernetics concerned with optimal decision-making, assuming an ideal and rational decision maker. When evaluating nutrients, we are concerned particularly with the part of the theory dealing with choice under uncertainty [14]. This approach is both conventional and established. The two central concerns of medical statistics, statistical hypothesis testing and statistical estimation theory, are special cases of the generalized decision theoretic approach.

In 1738, Daniel Bernoulli defined a utility function to solve a practical problem in identifying insurance risk for a ship's cargo. Here utility is defined to be a measure of the expected benefit and is central to the decision theoretic approach. A utility function is a function that represents benefit and satisfaction. In principle, given a complete set of statistical data for a particular nutrient, a utility function could be expressed in terms of the probabilities of benefit over the range of doses.

Given the utility function, a decision rule can be applied to the data to determine intake recommendations. A decision rule is a function that maps from the current state to the agent's decision or choice—in other words a function that tells you what decision to make

in a given set of circumstances. We will consider three such parameters: minimum intake, optimal intake and maximum intake. The minimum intake would be the minimum daily amount providing a specified least risk of deficiency. The intake that maximizes the expected benefit while minimizing the associated risk is the optimal intake. The maximum intake would be the maximum daily intake without a pre-specified risk of toxicity.

Typically, these parameters would be based on arbitrary standards using frequentist statistics. However, the determination of such parameters can be based on a number of methods of weighted evidence, including fuzzy logic, possibility theory, Dempster-Shafer theory and info-gap decision theory. These approaches can produce effective solutions based on rigorous methods. However, the complete class theorems indicate that all admissible decision rules are equivalent to a Bayesian rule combined with a utility function. In other words, for any decision rule an equivalent Bayesian rule, which may be better and is never worse, may in principle be found; when determined correctly, the appropriate Bayesian approach is equivalent or superior.

The decision theoretic approach is to use all information to find an optimal solution given the available data. The approach based on risk analysis currently in use or under consideration for nutrient intake recommendations ignores potentially important information because the methodology cannot accommodate it.

Risk analysis in decision theory

Risk analysis may be incorporated into decision theoretic methods: for example in minimax evaluation of the utility function. A minimax solution minimizes the maximum possible loss. Probabilistic risk analyses occasionally superimpose curves for effective dose, toxic dose and lethal dose to facilitate comparisons, a basic form of decision analysis. Notably, risk analysis is not normally included as a primary decision theoretic method.

Risk is described in a decision theoretic framework in terms of a risk function. The risk function is the integral of the loss function which relates, or maps, an event onto a real number representing the cost associated with the event. Loss functions are complementary to utility functions. Typically, for utility:

$$\text{Loss} = k - \text{Utility}$$

where k is an arbitrary constant. A valid risk analysis therefore implies estimation of the decision theoretic utility function based upon both expected costs and benefits. The attempt to incorporate benefits into risk analysis can be viewed as an acknowledgement of the necessity to incorporate a measure of utility. When using non-Bayesian methods such as minimax, loss functions may be based on the idea of regret—the difference between the most effective decision that could have been made were all the facts known and the actual decision [15]. This will lead to a different result from basing the loss function on negative effects. An analysis of a probabilistic risk function, based solely on the severity of the possible adverse consequences and the probability of occurrence of each consequence, is inadequate.

The Bayesian approach

The difference between Bayesian methods and the frequentist approach to risk analysis can be summarized by considering two questions: a frequentist will ask ‘How likely are these

data given a particular distribution of a parameter?', whereas a Bayesian will ask 'How likely is the particular distribution of the parameter given these data?' [16]. The first position requires us to assume a value for the unknown while the latter allows us to adjust this assumption based on evidence. The increased rigour available by incorporating all available evidence is essential for nutrient assessment where controversial limits can have potentially severe health consequences.

In the risk analysis being suggested, the results of experiments are typically fitted to pre-chosen distributions, such as the normal distribution. In the absence of evidence, a cumulative log-normal dose response curve is conventional, may be expected and is often assumed in toxicity testing [17]. Approximations to this curve occur over a wide range of toxins and other biological phenomena [18,19] and it has an associated theoretical basis in drug-receptor interactions and other biological functions. However, some nutrients, such as ascorbate, are postulated to have a transitional dose response and a rigorous analysis needs to encompass such information. If the distribution used to model the probability is incorrect, the statistical prediction is inaccurate.

In Bayesian analysis, one starts with assumptions about the probability of various results and then adjusts those assumptions based on the experimental data. This process is analogous to the 'hypothesize–experiment–revise' model of the scientific method. It has been suggested that Bayesian methods are particularly suited for small-scale 'proof of concept' trials, which are generally more accessible for analysis than large-scale clinical trials on the relative risks and benefits of a substance [20]. Data from such trials and benefit data generally are currently excluded from nutrient assessments [21].

The utility of decision rules

The primary question in the decision theoretic analysis of optimal nutrient intake and safety is the utility function and its derivation. Bayes' rule can be used to compute the set of potential utility functions. Although the approach is computationally demanding, this is no longer a constraint with the ubiquity of computing power.

Suppose a published experiment suggests a positive effect (+) for a nutrient at a specific intake. We are interested in the probability that the subjects have not suffered harm given the published results Pr (harm|+). The vertical bar means 'given that', so this term means the probability of harm given these positive results. This is called the data's positive predictive value or the posterior probability, as it is known after the experiment. However, this probability is not directly measured. Rather the sensitivity and specificity of the experimental results are estimated, where:

$$\text{sensitivity} = \Pr(+|\text{harm})$$

and

$$\text{specificity} = \Pr(-|\text{no harm})$$

Notice that the experimental results are both on the same side of the vertical bar given the (posterior) probabilities of harm, which is a clear indication that Bayes' rule is appropriate. Bayes' rule can now be stated in these terms:

$$\Pr(\text{harm}|+) = \text{sensitivity} \times \text{prevalence}/\Pr(+)$$

where harm prevalence is the incidence of the suggested harmful effects found in the population. Furthermore,

$$\Pr(+) = (\text{sensitivity} \times \text{prevalence}) + ((1 - \text{specificity}) \times (1 - \text{prevalence}))$$

Suppose that we estimate the sensitivity of the experiment to be 99% with a specificity of 90%. The reported level of harm in the subjects described in the experiment is estimated to be 0.01% given published statistics. Then

$$\Pr(\text{dis}|+) = (0.99 \times 0.01)/((0.99 \times 0.01) + (0.10 \times 0.99)) = 0.0909$$

where Pr (dis|+) is the probability of harm (or disease) given our estimates. Note that Bayesian calculations for a parameter cannot be made based on probabilities for a single clinical or experimental observation. Moreover, the requirement for estimates of disease prevalence in nutrition studies is not restrictive.

The utility function is based on all the available evidence. This is particularly important when making health recommendations for a large population. Even single clinical observations can be grouped to provide data for developing a utility function. This is current practice with adverse reactions but the same data gathering principles apply to hazards and benefits.

Specific nutrient forms

Each nutrient type from basic pharmacology will have a distinctive utility. Taking vitamin E as a specific example, this nutrient is defined in terms of a physiological response rather than as a specific chemical entity. The standard substances with vitamin E activity include the tocopherols and the tocotrienols, but other unrelated substances such as alpha-lipoic acid have vitamin E activity. Both the tocopherols and the tocotrienols exist in a large number of chemical forms as well as the unnatural structures found in synthetic 'vitamin E'. Differences between these forms of 'vitamin E' are well described in the literature. The benefits and toxicity of these chemicals differ, directly implying varied utility functions. It is not acceptable in pharmacology to group the benefits and risks of a group of drugs together; each molecular form has to be considered individually. The classic example of selective toxicity is thalidomide, in which one optical isomeric form, the smallest structural difference, was toxic and the other was not.

Example of the Bayesian approach

If we are to look at ascorbate as an example, the superiority of the Bayesian approach becomes immediately apparent. The current method would suggest an extremely low level of ascorbate intake, as it can lead to loose stools in some people at relatively low dosages. A Bayesian approach enables the inclusion of Hill's criteria directly into assessment of epidemiological evidence. With ascorbate the short excretion half-life of single doses above ~200 mg, of 30 minutes, can be used to evaluate otherwise invalid epidemiological claims [22]. Using a Bayesian decision-theoretic approach would include weighing the claimed benefits of high doses of ascorbate, which include reductions in heart disease and cancer, against putative risks.

We adopted a 'wisdom of crowds' approach to determining the utility function across a range of intakes for the healthy and the sick [23]. This approach is based on the emergence of behaviour from populations of independent rational decision agents [24,25]. We selected 101 students of computer sciences as intelligent people from a reasonably wide background with no specific knowledge of the topic. We provided the core scientific data on the intake of ascorbate renamed as 'Substance X'. The questions were provided with the data in the form of a questionnaire.

The respondents were asked to indicate 'How many units would you take each day for optimal health?' The result for this question is given in Figure 1. The students generally indicated that the data supported the suggestions for dynamic flow, i.e. intakes of 2 grams or above, rather than the official recommendations of 100 mg or less.

A second question concerned the dose required when ill. The respondents were asked 'If you were ill what dose would you consider optimal?' The results are given in Figure 2. These results are consistent with the suggestions of dynamic flow with the respondents indicating that intakes of between 8–200 grams were optimal.

This agent-based approach can clearly provide a quantitative and independent estimate of the utility function for particular nutrients. However, it is clear that the independence of the results is critically dependent on the selection of the agents, the unbiased presentation of the background data and the precise details of the questions. We note, however, that intelligent agents can be found to provide a suitable response; in this case, university computer science students are clearly capable of an independent and rational decision. The selection and presentation of the data should adhere to Bayesian principles and provide an indication based on information content rather than selected clinical trials. Finally, the questions can also be independently assessed for bias using a similar agent-based mechanism.

Rational ignorance

The concept of 'rational ignorance' was first introduced in reference to electoral politics. Most people do not have the time or ability to research and fully understand all the political

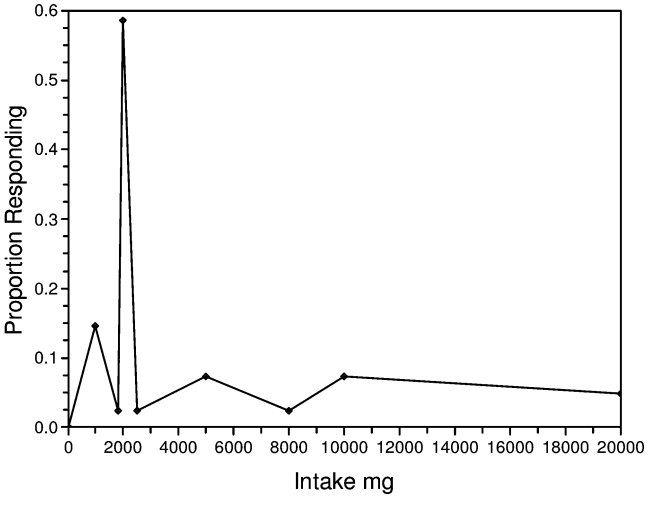

Figure 1. Graph of independent agents response to optimal intake of ascorbate. The peak is at an intake of 2 grams while a high proportion of the respondents indicate higher intakes.

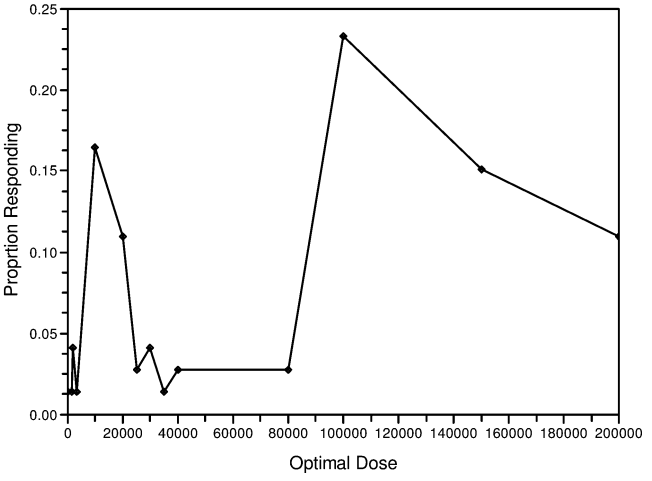

Figure 2. Graph of independent agents response to optimal intake during illness. During illness, the intakes considered optimal are largely in the dynamic flow range with a smaller number suggesting intakes in the gram level range.

issues of the day. Instead, they will form opinions on those subjects which they do understand and vote for those representatives who most agree with them on those issues. They then expect the representatives to vote on other issues in a way they would approve if they had all the facts. Ignorance is said to be rational when the cost of studying or otherwise determining the background information outweighs any potential benefit that could be reasonably expected to be gained from that decision [26].

In the case of setting nutritional limits, the potential benefits are large and include improved health, increased longevity and fewer deaths. The risks associated with an inaccurate limit include substantial damage to population health. Rational ignorance is not an appropriate foundation for assigning limits to nutritional intakes. Uncertainty may often be estimated using probability. Within the Bayesian decision theoretic paradigm presented here, the 'unknown' has a probability distribution. The known data is taken as given and probabilities are computed conditionally on known values.

Missing data can also be accounted for in many cases using the technique of multiple imputation. Multiple imputation is a three-step process. It involves creating multiple data sets by imputing the missing data. This process may be repeated several times using the predicted distribution given the missing data (a Bayesian Markov Chain Monte Carlo method is often used for this), analysing these sets separately and then combining the results of the analyses [27,28]. However, the method we have outlined based on computation by independent agents may be preferred.

Discussion

The main limitation on the analysis of nutrient intake in terms of both benefits and toxicity is the lack of information. Data over the whole intake range is often unavailable. A decision theoretic approach allows more of the available data to be incorporated, such as pooled data from clinical reports and case studies. However, the data for constructing a utility function will remain incomplete. We suggest the use of decision theoretic analysis to segment or integrate the utility function into minimum, beneficial and toxic sections. This

approach will allow more accurate determination of intake limits and provide estimates of their uncertainty or spread.

We have provided a simple example for ascorbate in which a utility function was provided using an approach based on rational, independent agents. Provided this approach is implemented with an approach that avoids selection, presentation and other forms of partiality, it will provide an unbiased assessment of both the benefits and risks associated with nutrients.

A decision theoretic analysis for optimum nutrition incorporates risk but is more comprehensive and complete. A rigorous analysis for nutrient safety should be able to adapt to accruing data and systematically allow for incomplete data. It needs to incorporate continual assessment of current data as well as make full use of the available historical information. Current approaches using expert opinion and risk analysis are focused on hazards and cannot give an adequate analysis of nutrients, which by definition involve benefits. Here we outline an optimal approach to optimal nutrition.

Note

1. The evidence relating smoking to lung and other cancers has largely satisfied Hill's rules.

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References

1. Editorial. Nature Reviews: Drug Discov 2006;5:3.
2. Berry SM, Berry DA, Natarajan K, Lin CS, Hennekens CH, Belder R. Bayesian survival analysis with nonproportional hazards: meta-analysis of combination pravastatin-aspirin. J Am Stat Assoc 2004;99:36–44.
3. Edwards W, Lindman H, Savage LJ. Bayesian statistical inference for psychological research. Psychol Rev 1963;70:193–242.
4. Berry DA. Statistics: a Bayesian perspective. California: Duxbury; 1996.
5. Hickey S, Roberts H. Ascorbate: the science of vitamin C. Morrisville, NC: Lulu Press; 2004.
6. Codex procedural manual. 15th ed. p 44. Codex Alimentarius Commission, Rome, Italy.
7. Hattis D, Baird S, Goble R. A straw man proposal for a quantitative definition of the RfD. Drug Chem Toxicol 2002;25(4):403–36.
8. Schiero L. Environmental risk analysis: a review of public policy issues. Congressional Report Services, 98-618 ENR, 15 July 1998.
9. Codex Committee on Food Additives and Contaminants (CCFAC). Discussion paper on the guideline levels for methylmercury in fish, CX/FAC 06/38/37, Thirty-eighth Session, The Hague, the Netherlands, 24–28 April 2006.
10. Codex Committee on Food Additives and Contaminants (CCFAC). Discussion paper on the application of risk analysis to the work of the Codex committee on nutrition and foods for special dietary uses, CX/NFSDU 06/28/9, Twenty-eighth Session, Thailand, 28 September 2006.
11. Hill AB. The environment and disease: association or causation? Proc R Soc Med 1965;58:295–300.
12. Goldstein A, Aronow L, Kalman SM. Principles of drug action. New York: John Wiley and Son; 1974.
13. Lehmann EL. Some principles of the theory of testing hypotheses. Ann Math Stat 1950;21:1–26.
14. Lee S, Meeden G. A minimal complete class theorem for decision problems where the parameter space contains only finitely many points. Metrika 1994;41(1):227–32.
15. Savage LJ. The foundations of statistics. 2nd rev ed. New York: Dover; 1972.
16. Lauder LJ. Bayesian methods in health technology: assessment—the case of clinical trials. International Chinese Statistical Association Bulletin; July 2000.
17. Committee on Toxicology. National Research Council Review of Acute Human-Toxicity Estimates for Selected Chemical-Warfare Agents. Commission on Life Sciences, Washington, DC. National Academies Press; 1997.

18. Brodsky A. Cumulative lognormal distributions of dose-response vs. dose distributions. Proceedings of the 10th International Congress of the International Radiation Protection Association, Hiroshima, Japan; 14–19 May 2000.
19. Brodsky A. Cumulative lognormal distributions of dose-response vs. dose distributions. Proceedings of the 47th Annual Conference on Bioassay, Analytical and Environmental Radiochemistry, Honolulu, Hawaii, 4–8 November 2001.
20. Maurer W. Creative and innovative statistics in clinical research and development. Methods Inf Med 2005;44(4):551–60.
21. Hickey S, Roberts H. Ridiculous dietary allowance. Morrisville, NC: Lulu Press; 2004.
22. Hickey S, Roberts H. Misleading information on the properties of vitamin C. PLoS Med 2005;2(9):e307.
23. Surowiecki J. The wisdom of crowds. New York: Doubleday; 2004.
24. Parsons S, Wooldridge M. Game theory and decision theory in multi-agent systems. J Autonomous Agents Multi-Agent Syst 2002;5(3):243–54.
25. Hayes CC. Agents in a nutshell-a very brief introduction. IEEE Trans Knowledge Data Eng 1999;11(1):127–32.
26. Downs A. An economic theory of democracy. New York: Harper; 1957.
27. Schafer JL, Olsen MK. Multiple imputation for multivariate missing-data problems: a data analyst's perspective. Multivariate Behav Res 1998;33(4):545–71.
28. Schafer JL. Multiple imputation: a primer. Stat Methods Med Res 1999;8(1):3–15.