HARVARD UNIVERSITY
Graduate School of Arts and Sciences

THESIS ACCEPTANCE CERTIFICATE

The undersigned, appointed by the

Division

Department

Committee on Higher Degrees in Health Policy

have examined a thesis entitled

Improving Value of Information Analysis
in Health Risk Management

presented by Fumie Yokota

candidate for the degree of Doctor of Philosophy and hereby certify that it is worthy of acceptance.

Signature .....
Typed name James K. Hammitt (chair)

Signature .....
Typed name David M. Cutler

Signature .....
Typed name George M. Gray

Signature .....
Typed name Kimberly M. Thompson

Date April 30, 2003

Improving Value of Information Analysis in Health Risk Management

A thesis presented

by

Fumie Yokota

to

The Committee on Higher Degrees in Health Policy

in partial fulfillment of the requirements
for the degree of
Doctor of Philosophy
in the subject of
Health Policy

Harvard University
Cambridge, Massachusetts

May 2003

ProQuest Information and Learning Company
300 North Zeeb Road
P.O. Box 1346
Ann Arbor, MI 48106-1346

Research Committee: James Hammitt (chair), David Cutler, George Gray, and Kimberly Thompson

Author: Fumie Yokota

Improving Value of Information Analysis in Health Risk Management

Abstract

Value of information (VOI) analysis is a decision analytic approach for evaluating the benefit of collecting additional information to reduce or eliminate uncertainty in a specific decision making context. Though experts have encouraged the use of a VOI approach in framing complex decision-making problems where uncertainties are large and stakes are high, formal VOI analysis do not yet play a major role in regulatory decision-making.

Section 1 of the thesis explores the evolution of the VOI methods in health risk management through a comprehensive content analysis of VOI applications in the peer reviewed health literature. Chapter 1 shows the evolution of the methodology and advances in computing tools that allow analysis of problems with greater complexity. The analysis shows a lack of standardization of reporting methods and results, and little cross-fertilization across topic areas. Chapter 2 narrows the focus to applications in environmental health risk management (EHRM) and provides risk analysts and decision scientists with some guidance on how to structure and solve VOI problems related to EHRM decisions.

Section 2 applies the VOI framework to a tiered toxicological testing program and explores the question: How much should uncertainty about risk be reduced before action

is taken? Chapter 3 examines the optimal testing strategy from the perspective of a net benefits maximizing decision maker who is able to regulate chemical exposures based on predictions of carcinogenicity from lower tier tests. The analysis shows that both the level of expected human exposure and economic considerations such as control costs for reducing exposure are critical in the decision to pursue further testing, and that for a wide rage of exposures and costs, testing is not optimal. Furthermore, for a set of plausible exposure and control costs, it is optimal to regulate without further testing. Chapter 4 explores the optimal testing strategy of a constrained decision maker who, absent applicable human data, cannot regulate without bioassay data on a specific chemical. The analysis shows that delaying action until all tests results are available can lead to substantially lower societal net benefits for a large range of environmental exposures

Contents

List of Figures

List of Tables

There are those who believe that there is something "cold and inhuman" about rational analysis. I believe that to be human is to be reasoning as well as compassionate. My ideal here is Buddha:

> Perhaps the most striking thing about him, to use the words of J. B. Pratt, was his combination of a cool head and a warm heart, a blend which shielded him from sentimentality on the one hand and indifference on the other. He was undoubtedly one of the great rationalists of all times, resembling in this respect no one as much as Socrates. Every problem that came his way was automatically subjected to the cold, analytical glare of his intellect. First, it would be dissected into its component parts, after which these would be reassembled in logical, architectonic order with their meaning and import laid bare.
>
> H. Smith, *The Religions of Man*

Perhaps Buddha was the first decision analyst.

Ronald Howard, "An Assessment of Decision Analysis"

Acknowledgements

I am grateful to Ph.D. Program in Health Policy for the opportunity to learn from an amazing group faculty and students, and to develop both research and teaching skills. Special thanks to my dissertation committee members Jim Hammitt, David Cutler, George Gray, and last but not least, Kim Thompson (my role model), for their insightful comments, support, and patience. In addition, I thank my former advisor and current boss, John Graham, for bringing me into the program and for providing an amazing opportunity to work for the OMB as a decision scientist.

The dissertation research would not have been possible without the generous support of two organizations. I thank the U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Research, for providing three years of support through the STAR Graduate Fellowship. I would also like to thank Resources for the Future for the Joseph L. Fisher Doctoral Dissertation Fellowship for providing support for the last few months of my research.

Thanks to my fellow students at HCRA: Kevin, Sally, Elena, Julia, Amy, Edmond, Andy and Ying for the camaraderie. My Stanford people: Dawn, Smeeta, Courtney, and Adrienne for their unwavering support. My squirrels: Kristen, Heather, Rebecca, and Ginni for the laughter. My family (Dad, Mom, Mitsue, Masae), and extended family (Diane, G&G Romp, et al.) for their love and support. You all made the arduous process of completing a Ph.D. more bearable and, dare I say, fun at times. Most of all, I thank my husband Ben for putting up with the pugnacious one. I could not have done this without you.

Section 1: Value of Information Literature Analysis

Chapter 1: Value of Information Literature Analysis - A Review of Applications in Health Risk Management

Fumie Yokota and Kimberly M. Thompson

Submitted to *Medical Decision Making*

Abstract

This paper provides the first comprehensive review of value of information (VOI) analyses related to health risk management published in English in peer-reviewed journals by the end of 2001. VOI analysis is a decision analytic technique that explicitly evaluates the losses from errors in decision making due to uncertainty and evaluates the benefit of collecting additional information to reduce or eliminate uncertainty. Through a content analysis of VOI applications, this paper characterizes various attributes of VOI applications, shows the evolution of the methodology and advances in computing tools that allow analysis of problems with greater complexity, and suggests some standardization of reporting methods and results. Our analysis shows a lack of cross-fertilization across topic areas, and the tendency of papers to focus on demonstrating the usefulness of the VOI approach rather than applications to actual management decisions.

Key words: value of information, Bayesian decision theory, preposterior analysis, data worth, health risk management

1. Introduction

Value of information (VOI) analysis is a decision analytic approach for evaluating the benefit of collecting additional information to reduce or eliminate uncertainty in a specific decision making context. It answers the question: how much should we be willing to pay for additional information? Recent reports from experts panels suggest that the VOI approach can be particularly useful in framing complex decision-making problems where uncertainties are large and stakes are high,[1,2] but the complexity of models make solving many VOI problems difficult. Advances in computing technology and simulation techniques appear to be allowing analysts to more efficiently obtain reliable answers. Unfortunately, researchers do not necessarily benefit from progress made in other fields since different disciplines use different terminology, and the studies are published in a wide variety of journals.

This paper provides the first comprehensive review of VOI applications related to health risks, and summarizes important methodological advances. Through a content analysis of VOI applications, this paper characterizes various attributes of VOI applications, shows the evolution of the methodology and advances in computing tools that allow analysis of problems with greater complexity, and identifies remaining analytical challenges including issues such as the valuation of attributes. Section 2 defines VOI analysis and provides references on the basic methods and properties of VOI analyses, section 3 summarizes the content of the value of information literature analysis (VOILA) database, section 4 provides a discussion of results, and section 5 contains concluding remarks.

2. Value of Information Analysis

Described in some of the earliest publications on decision analysis decades ago,[3-8] VOI is defined as the difference between the expected utility of the optimal action given new information, and the expected utility of the optimal action given information available prior to collecting additional information, under an expected utility maximization framework. As Howard[6] noted, "no theory that involves just the probabilities of outcomes without considering their consequences could possibly be adequate in describing the importance of uncertainty to a decision maker." VOI analysis makes losses from errors in decision making due to uncertainty explicit and identifies the "best" information collection strategy as one that leads to the greatest net benefit to the decision maker (DM). In the medical decision making literature, Weinstein et al.[9] outlined the application of the concept where health is the only outcome of concern, and Phelps and Mushlin[10] outlined a framework in medical technology assessment which takes into account the cost of the technology.

VOI analysis requires modeling the available set of actions, prior belief about the uncertain input, belief about the accuracy of the information collected, the consequences of actions given the true value of the uncertain input, and the DM's preferences. The decision can be modeled as making a choice between a discrete set of actions or selecting an optimal level from a continuous decision variable (e.g., amount of soil to dredge). The prior belief about the uncertain input and the accuracy of information collected must be characterized using probability distributions. These input distributions can be a discrete set of value-probability pairs when the input values are

discrete, a parametric distribution function that is uniquely defined by a set of parameters such as the mean and standard deviation, or an empirical distribution function based on a data set of observed values.[11] The analysis must quantify all relevant consequences of actions from the perspective of the DM, and value monetary and non-monetary outcomes using a common metric (typically dollars in the context of VOI).

In a review of general results, Hilton[12] found no general monotonic relationship between VOI and action flexibility (i.e., increasing actions available to the DM), level of DM's risk aversion, DM's wealth, or the level of initial uncertainty in the prior distribution, while emphasizing the "model-specificity and meagerness of the general results in this area." The key insight from these properties is that an analyst cannot "conservatively" model a VOI problem to bias VOI towards a low value; each component of a VOI must be modeled to reflect the best available knowledge. By definition, VOI measures the increase in utility given information and thus for information about an uncertain input to have value it must at a minimum change the DM's optimal action in some scenarios (i.e., if the DM's action is always the same with and without information so that his or her utility does not change, then the VOI is zero for that particular decision context). The cost of collecting information must be lower than the VOI or there will be a net decrease in welfare if information is collected.

In their seminal book, *Applied Statistical Decision Theory*,[5] introduced the concept of the expected value of perfect information (EVPI). EVPI is the difference in expected utility under perfect information (for each possible value of the uncertain input, s, the DM takes an action, a, that maximizes utility) and the expected utility under prior

information (the DM chooses the action which yields the highest expected utility without additional information):

$$EVPI = E\{\max_a U(a,s)\} - \max_a E\{U(a,s)\}$$

Calculating the expected utility under perfect information requires the assessment of the optimal action for all possible values of *s*, and then finding the weighted average of the resulting utility values over the prior belief about the likelihood of each event. Howard[5] also use the concept of opportunity loss, or regret, to explain EVPI. Under uncertainty, no matter what action the DM chooses to take, there is a chance that a different action would have yielded a higher utility level, once the true state of the world is revealed (barring a dominant strategy). The difference between utility given *a priori* action and *a posteriori* optimal action (a^*) is the opportunity loss of taking action under uncertainty. The action that minimizes expected opportunity loss also maximizes expected utility:

$$\min_a EOL = \min_a [E_s\{U(a^*,s) - E_s\{U(a,s)\}] = E_s\{U(a^*,s)\} - \max_a E_s\{U(a,s)\} = EVPI$$

If the DM's *a priori* action minimizes EOL, EOL is equivalent to EVPI. Therefore, EVPI can be interpreted as the loss or regret associated with decision errors. One note of caution is that VOI can underestimate true societal value of perfect information since there may be positive externalities from information collection (i.e., additional decisions not directly modeled that may be improved from the information collected). In addition, collecting additional information may lead to surprises that show some basic assumptions may be incorrect such as observing input values outside the bounds of prior belief [13,14].

An innovation introduced by Howard[6] was the concept of "clairvoyance" about a single uncertain input when multiple uncertainties exist in a model, which some

researchers[15] refer to as the expected value of perfect X information (EVPXI) (where X is a particular uncertain model input). EVPXI is the difference between the expected utility from taking the optimal action based on the revelation of the exact value of one uncertain input, and the expected utility from the optimal decision given only the prior information. EVPXI is a useful measure for determining the relative importance of resolving uncertainty between inputs, and has been proposed as the ideal measure for sensitivity analysis in decision analytic problems.[16,17] EVPXI has a peculiar non-additive property such that the sum of EVPXI from all sources of uncertainty do not necessarily sum to the total EVPI for resolving all uncertainties simultaneously.[6,18,19] This property highlights the importance of explicitly considering different sets of information collection activities since the exact value of information for combined sets of information cannot be inferred from total EVPI or individual EVPXIs.

In most cases obtaining perfect information may not be possible, therefore the relevant measure of information value is the expected value of sample information (EVSI) or the expected value of imperfect information (EVII). EVSI is the difference between the expected utility under imperfect information (for each possible value of sample information, x, the DM takes an action, a, that maximizes utility) and the expected utility under prior information (the DM chooses the action which yields the highest expected utility without additional information):

$$EVSI = E_x[\max_a E_{s|x}\{U(a,s)\}] - \max_a E_s\{U(a,s)\}$$

The calculation of EVSI requires a Bayesian preposterior analysis, so called since a decision must be made before the information is collected and sample outcome is known. It requires constructing posterior probabilities for all possible values of experimental

results, finding the expected utility for taking the optimal action for each experimental result, and taking a weighted average of the resulting utility values over the prior belief about the likelihood of each result.

Since EVPI is a simpler calculation, it can serve as a useful upper bound for the value of additional sample information in a particular decision context; if the cost of collecting imperfect information is greater than the EVPI, one should not collect the information. However, as Howard[7] states in an early application of the EVPI technique to a simple bidding problem, "even an elementary problem of this type may be far from trivial in the familiarity with probabilistic operations required to derive the results one would like to examine." Given the complexity of solving just the underlying probabilistic decision analysis problem, it is not surprising that very few VOI applications exist.

Analysts can use several strategies to obtain or estimate the solution to a VOI problem.[20] If the uncertainty is characterized with a discrete distribution, the simplest applications can be solved with "pencil and paper" by rolling back the decision tree and for more complex models analysts can use off-the-shelf software using decision trees to solve the problem. For a small number of carefully chosen models with continuous distributions, simple applications may have closed form solutions that yield exact values. For more complex problems with continuous inputs, the strategies include simulation, analytical approximation methods such as the method of moments that use Taylor series expansions, or discretization of the continuous inputs using methods such as Gaussian quadrature[21] so that the problem can be solved as if the model inputs were discrete. As the complexity of the decision problem increases, using a traditional decision tree with

discrete inputs can become intractable since this strategy is exponential in computational effort (e.g., it requires m^n computations for m inputs and n different values for each input). In contrast, simulation, which randomly samples m model input "draws" for each iteration for n iterations, is linear in computational effort (mn), with the precision of the estimate increasing as n increases.

3. Survey of VOI Applications

The VOILA database includes only studies that meet the following entry criteria: (1) published in a peer reviewed journal by the end of 2001, (2) written in English, (3) authors calculate the key components of EVPI or EVSI, and (4) the decision involves management of a health risk. We conducted a literature search using three strategies: first, we search for key words such as "value of information," "information value," "value of perfect information," "value of sample information," "data worth," "worth of data," and "preposterior analysis" in electronic indexes (e.g., ISI Web of Science, Medline); second, we search cited reference in all identified VOI applications; and third, we searched citing references of all identified VOI applications using the ISI Web of Science. (The appendix lists all of the information that we collected about each application and the reader can gain access to the database from www.voila.harvard.edu).

We identified a total of 44 VOI applications in 42 papers[16,17,22-61] that met our entry criteria (Felli and Hazen[16], include three separate applications in one paper). Table 1.1 lists the 23 journals that published the applications and notes the number of papers found in each journal in parentheses. The journals cover a wide range of topics, most publishing only one application, and only five journals contained three or more

papers. Figure 1 plots the cumulative number of VOI papers published over the last three decades.

We separated the applications into two fields and five topic areas to compare attributes across different disciplines. Table 1.2 provides a list of the tables by topic area along with summary information about some of the attributes that we recorded in the database (see the complete list of these in the appendix or on the website). The medical field applications (18 papers) cover the topics of:

- general medical care applications that focus on evaluation of diagnostic technologies to improve treatment decisions and on resolving uncertainty in a cost-effectiveness analysis of treatment decisions (9 papers with 11 applications, 25% of the database), and
- clinical trials that focus on applications that seek to optimize the value of information obtained in a trial by setting parameters of the trial such as the number of participants and duration (9 papers, 20% of the database).

The environmental field applications (24 papers) cover the topics of

- general environmental health applications that focus on pollution control decisions to improve health that were not hydrogeologically- or toxicologically-oriented (9 papers, 20% of the database),
- water contamination (20%) applications that focus on remediation decision in ground water contamination (9 papers, 20% of the database), and
- toxicology applications that focus on optimal testing strategies for determining the carcinogenicity of a chemical (6 papers, 14% or the database).

Although the VOI technique was developed in the 1960's, the first application in the environmental filed did not appear in journal publications until 1976, and the first medical application did not appear until 1981. As shown in Figure 1, environmental applications steadily increased the late 1980's to early 1990's, but appear to have flattened out in the last few years. In contrast, the medical applications did not catch on until the mid 1990's but has been increasing rapidly in the last few years.

Exploring the attributes provided in Table 1.2, most of the applications had a limited set of actions to choose from, with 61 percent of all applications only having two actions (i.e., do nothing and do something). However, rather than a discrete set of actions, seven applications in the general environmental health and water contamination areas developed models that focused on finding an optimal level of pollution control given a particular control technology. Overall, applications we classified as general environmental health had the highest average number of actions. Further, a quarter of the applications did not consider any information collection strategies since these applications considered only the value of perfect information, while another quarter only considered collecting some information or none. However, 12 applications (27%) considered the optimal level of information collection and thus considered infinite information collection strategies. Twenty-five of the applications (57%) had only one uncertain input in their analysis, and among the five topic areas, general environmental health and medical care applications had the highest average number of uncertain inputs.

Overall, about half of the applications we classified as general environmental health calculated only the expected value of perfect information (i.e., EVPI or EVPXI) and the other half only the expected value of sample information (i.e., EVSI or EVSXI).

On the other hand, applications in toxicology focused mainly on expected value of sample information. Very few applications calculate the value of information from one of the sources of uncertainty (i.e., EVPXI or EVSXI) (23%); a finding that is not surprising given that the majority of applications included only one source of uncertainty in their analysis.

We observed a shift toward the use of simulation as a solution strategy with nearly a third of the papers using simulation and all of these since 1990. As shown in Table 1.2, eleven applications (25%) used a discrete distribution to characterize uncertainty and used simple algebra or a discrete tree to solve the VOI problem, six applications (14%) used a closed form solution, two applications used a method of moments approach, seven applications (16%) used various methods to discretize continuous distributions, and for three applications we could not determine the solution strategy based on the information in the published paper. We tested whether applications that used simulation as a solution strategy had higher number of uncertain inputs in their analyses using Spearman's rank correlation and found a statistically significant positive rank correlation ($\rho = 0.503$, $P = 0.0005$). In addition, simulation has a statistically significant positive rank correlation with whether an analysis includes the calculation of EVPXI ($\rho = 0.407$, $P = 0.0004$).

We also tracked the citations and noted that little cross-fertilization exists between analysts who work in different fields; only 9 papers (21%) cite a VOILA article outside of their topic area. Overall, only 70% of the papers cite a previously published VOILA article and 40% of papers cite one of the original decision analysis texts by Howard or Raiffa and colleagues.[3-8]

Table 1.3 summarizes our overall findings from the attributes of VOI applications that we recorded by topic area by providing the counts of the number of applications in each field and overall that were characterized by the attribute listed in the left-most column. Nearly half of the papers in the VOILA database did not use the terminology "information value," "value of information," "value of perfect information," or "value of sample information" in their title, abstract, or keyword. Nearly a quarter did not use the term in the text when describing the analysis. In terms of motivation for the decisions and perspective, general environmental health, toxicology, and clinical trial applications focused primarily on societal level policy decisions and the societal perspective, while most water contamination applications focused on firm level decisions and firm perspective, and the medical care applications almost exclusively on individual treatment decisions although these were generally split between the individual patient perspective and a societal perspective.

All of the applications explicitly or implicitly assumed risk neutrality for the DM. General environmental health and toxicology applications used a framework of either minimizing total costs (CBA) or maximizing total benefits (BCA), while medical applications most often used a cost-effectiveness analysis (CEA) approach. Although the near equivalence of CBA/BCA and CEA has been established,[62] the methods are distinct in that CBA/BCA requires the separate monetization of health effects (e.g., morbidity, mortality), while the CEA method sets a value per unit of "effectiveness" that combine morbidity and mortality effects in a single unit, most often Quality Adjusted Life Year (QALY) as recommended by the panel on cost-effectiveness.[63] In the general environmental health applications, three of the papers used a cost minimization approach

to meet an exogenously determined health based standard. All but one of the water contamination applications was modeled similarly as a cost minimization problem to meet a specific external standard. In the clinical trial applications, one analysis from a health plan's perspective considered only the cost and none of the health benefits. In the general medical care applications, three of the applications assumed no cost to the patient and considered only non-monetized health benefits, while one application considered only costs in the analysis.

Surprisingly few applications reported whether all monetary values were adjusted to a common year dollar (25%). In addition, only about half of the applications reported a non-zero value for a discount rate used in the analysis with values ranging from 2.5% to 10% for their base case analyses. Most applications calculated the information as a one-time benefit rather than explicitly considering the time horizon for how long the information that is collected will be useful in decision making. Likewise, only about a quarter of the applications aggregate the value of information over the entire population that would benefit from the reduction in uncertainty.

A handful of applications valued only a crude lump sum value for consequences of various outcomes (e.g., lose $10 million for failing to regulate a carcinogen, lose $400,000 for incorrectly treating a health patient for cancer). The 12 applications (27%) that use a CEA framework, use a variety of "effectiveness" units, but the most common are QALYs. Table 1.4 shows the value of QALYs used in the base case VOI calculation in these applications. As the table shows, the nominal values range from $25,000 to $100,000. A cut-off of $50,000 is a very popular value, however, when this value is adjusted to 2002 dollar using the CPI, we can see that based on when the analysis is

conducted, the value ranges from $51,000 to $62,000 (note if a year dollar was not reported, we assumed the publication year). As Table 1.5 shows, there is an even wider range of baseline values for premature death used in applications with a CBA/BCA framework; once adjusted to 2002 dollars, the values range from $94,000 to $12 million.

As shown in Table 1.3, morbidity effects were specifically monetized in only three studies. Only one application valued ecological damage. All of the applications, except six that used a crude lump sum total value for consequences and three medical applications that considered only health effects specifically, value the cost of pollution control or treatment of disease. Only 28 of the applications (64%) specifically valued the cost of collecting information.

In characterizing uncertainty, twelve of the applications used a binary input (e.g., carcinogenic or nor, disease positive or not) and used discrete probability distributions. Only five applications (11%), all in the water contamination topic, specifically model variability distinct from uncertainty using a distribution. In addition, only eight applications (18%) use subgroups in their analyses to reflect variability in the population. The toxicology, water contamination, and general medical care applications with binary uncertain variables used discrete distributions, while general environmental health and clinical trial applications tended to use parametric distributions in characterizing uncertainty. Only three applications (7%) used an empirical distribution. Sixteen applications (36%) used only hypothetical/synthetic data for characterizing uncertainty. Most applications used empirical data (57%), very few used expert judgment (7%) or model output (9%) as data sources for characterizing uncertainty.

A handful of applications (14%) used a threshold approach to determine conditions under which VOI, net of information collection costs, would be positive rather than calculate VOI directly. In contrast, about a quarter of the applications used maximizing VOI as the criteria for deciding the optimal information collection strategy. Many applications (34%) characterize EVPI as an overestimate of true VOI since it analyzes the collection of hypothetical perfect information. Surprisingly few (7%) discuss the possibility that the EVPI is an underestimate of true value of perfect information, ignoring the possibility that information could be useful in other decision contexts or "surprises" not explicitly modeled in the analysis could be gained from sampling.

4. Discussion

The VOILA database represents the first synthesis of VOI analyses in health risk management. The review of these analyses shows that there is little cross fertilization between fields; different fields use different terminology, papers are published in a wide variety of journals, and authors rarely cite applications in other fields. The difficulty in locating VOI applications underscores the importance of gathering a comprehensive database to serve as a resource for decision analysis practitioners and decision makers who want to explore the use of VOI techniques. A separate analysis focuses on computational issues and the narrow environmental health risk set of applications.

The review shows that VOI analyses do not appear to follow a linear progression; clusters of analysts tend to build on previous work within a field, but the progress does not necessarily spread widely even within the field. For example, Reichard and Evans[54] explain the concept of EVPXI and include its calculation in their analysis, however,

James et al.,[60] also published in the water resources literature, use an inferential approach based on the Kolmogorov-Smirnov statistic to rank the importance of uncertain inputs in contributing to opportunity loss. It is not clear whether the authors were unaware of the EVPXI approach, or they felt their approach was some how superior, but it is curious to revert to an inference approach when one can directly calculate the relative contribution of each uncertain input to decision error through EVPXI analysis. Complexity of models, as measured by the number of uncertain inputs, does not appear to be increasing over time (i.e., no statistically significant correlation with publication date), however, it is correlated with whether an application uses simulation or not. Like wise, simulation appears to be allowing analysts to calculate EVPXI more easily.

The applications in the VOILA database primarily provide illustrations of VOI methods, and they do not typically represent a true application to a real-world situation. This tendency of the analysis in part explains why many of the applications include only once uncertain input, use only hypothetical data, use generic values for consequences, and do not include a specific dollar year or a discount rate. However, the failure to report key information for the analysis (e.g., perspective, discount rate, year dollar, time horizon, solution method) sets a bad precedent for the field. VOI literature would benefit from some standardization of reporting methods and results. All applications should at minimum report a table of values used in the analysis including parameters of distributions functions and their sources, and a discussion of the strategy used to solve the VOI problem. Without this information, it is difficult for analysts to learn from each other, and replication of the results becomes impossible. The list of attributes provided in

this content analysis may serve as a starting point for experts to build a reporting standard.

One area that gets too little attention in the current VOI literature is the issue of under estimating VOI. Although many applications characterize EVPI as an "upper bound" for EVSI, they ignore the limitations in their analyses that make the calculated EVPI an under estimate of true value of perfect information in a larger context. Threshold analyses evaluating conditions that would yield positive information value net of costs may be a good first cut analysis, but from the perspective of a DM who maximizes utility, the optimal information collection strategy is the one that yields the highest value, not the point where the benefits are out weighed by costs. In addition, roughly 40% of the applications do not take a societal perspective in their analyses, which may greatly underestimate the overall value of the information collected. For example, the clinical trial applications analyzed from the provider's perspective do not account for the benefit of the information collected to other users of the drug or technology under study[33,36]. None of the papers directly address the possibility that additional information will show current characterization of uncertainty to be overly confident such that it may lead to an under estimation of the benefit of information collection in some cases.

Another area that would benefit from more discussion by analysts is the issue of valuing outcomes. Although cost effectiveness analyses on medical diagnostic technologies abound, very few place a value per unit of effectiveness that would allow the calculation of VOI. In addition, as illustrated by the valuation in the medical applications in the VOILA database, the lack of consistency in the value per QALY

across analyses suggests that analysts need to think more about the impact of time. As the popular nominal cut-off of $50,000 illustrate, using the same round-number cost-effectiveness threshold year after year, analysts are systematically devaluing the real value of a QALY. Similarly, environmental applications which tend to focus on "lives saved" as the metric for outcomes often ignore the magnitude of life extension so that, unlike a QALY approach, it under values reducing risks to children compared to the elderly. In addition, the applications do not necessarily value morbidity effects so that improving chronic illnesses that do not lead to immediate death would be under valued. Similarly, environmental applications often have ecological benefits beyond human health improvements that are often ignored in the analyses.

The literature to date, in general, have adequately explored the basic components of VOI analysis and methods, and have illustrated the benefit of a VOI approach to inform research planning decisions. What is needed are more applications to specific management decision to address the important remaining challenges such as how to best characterize uncertainties in the decision models and how to solve increasingly complicated VOI calculations with large number of uncertain inputs as well as inputs which vary over the target population.

5. Conclusion

As Howard[6] notes, "placing a value on the reduction of uncertainty is the first step in experimental design, for only when we know what it is worth to reduce uncertainty do we have a basis for allocating our resources in experimentation designed to reduce the uncertainty." VOI analysis is an important input to decision making for any

program or policy that considers collecting information to manage health risks. The comprehensive review in this paper provides the first synthesis of how analysts have analytically approached answering the question: how much should we be willing to pay to resolve uncertainty? The VOILA database provides a comprehensive reference for analysts and decision makers who wish to use this approach that may help in efforts to move past the demonstration phase of VOI into its real use in the context of actual health risk management decisions. In addition, this review provides an opportunity for researchers focused in one health risk area to take advantage of opportunities to learn from and build on the work of others. Significant methodological issues remain in the context of solving larger and more complicated problems focused on assessing the value of actual sample data to be obtained and to perform some of the complicated dynamic Bayesian analyses that may result. Nonetheless, with the increasing evolution of simulation strategies, the basic methods required to solve even fairly complex VOI problems and examples of such solved problems can be found in the literature if analysts know where to look.

References

1. Commission on Risk Assessment and Risk Management, *Framework for Environmental Health Risk Assessment* (Presidential/Congressional Commission on Risk Assessment and Risk Management, Washington, DC, 1997).

2. National Research Council, *Understanding Risk: Informing Decisions in a Democratic Society* (National Academy Press, Washington, DC, 1996).

3. H. Raiffa, *Decision Analysis: Introductory Lectures on Choices under Uncertainty* (Random House, New York, NY, 1968).

4. J. W. Pratt, H. Raiffa, and R. O. Schlaifer, *Introduction to Statistical Decision Theory* (MIT Press, Cambridge, MA, 1995). (Originally distributed in 1965 by McGraw-Hill in mimeograph form)

5. H. Raiffa and R. O. Schlaifer, *Applied Statistical Decision Theory* (Division of Research, Graduate School of Business Administration, Harvard University, Cambridge, MA, 1961).

6. R. A. Howard, "Information Value Theory," IEEE Transactions on Systems Science and Cybernetics **SSC2** (1), 22-26 (1966).

7. R. A. Howard, "Value of Information Lotteries," IEEE Transactions on Systems Science and Cybernetics **SSC3** (1), 54-60 (1967).

8. R. A. Howard, "The Foundations of Decision Analysis," IEEE Transactions on Systems Science and Cybernetics **SSC-4** (3), 211-219 (1968).

9. M. C. Weinstein, H. V. Fineberg, A. S. Elstein, H. S. Frazier, D. Neuhauser, R. R. Neutra, and B. J. McNeil, *Clinical Decision Analysis* (W.B.Saunders Company, Philadeliphia, PA, 1980).

10. C. E. Phelps and A. I. Mushlin, "Focusing Technology-Assessment Using Medical Decision-Theory," Medical Decision Making **8** (4), 279-289 (1988).

11. K. M. Thompson, "Developing univariate distributions from data for risk analysis," Human and Ecological Risk Assessment **5** (4), 755-783 (1999).

12. R. W. Hilton, "The Determinants of Information Value: Synthesizing Some General Results," Management Science **27** (1), 57-64 (1981).

13. J. K. Hammitt, "Can More Information Increase Uncertainty?," Chance **8** (3), 15-17, 36 (1995).

14. J. K. Hammitt and A. I. Shlyakhter, "The expected value of information and the probability of surprise," Risk Analysis **19** (1), 135-152 (1999).

15. K. P. Brand and M. J. Small, "Updating uncertainty in an integrated risk assessment: Conceptual framework and methods," Risk Analysis **15** (6), 719-731 (1995).

16. J. C. Felli and G. B. Hazen, "Sensitivity analysis and the expected value of perfect information," Medical Decision Making **18** (1), 95-109 (1998).

17. J. C. Felli and G. B. Hazen, "A Bayesian approach to sensitivity analysis," Health Economics **8** (3), 263-268 (1999).

18. K. M. Thompson and J. D. Graham, "Going beyond the single number: Using probabilistic risk assessment to improve risk management," Human and Ecological Risk Assessment **2** (4), 1008-1034 (1996).

19. D. Samson, A. Wirth, and J. Rickard, "The Value of Information from Multiple Sources of Uncertainty in Decision-Analysis," European Journal of Operational Research **39** (3), 254-260 (1989).

20. M. G. Morgan and M. Henrion, *Uncertainty: A Guide to Dealing with Uncertainty in Quantitative Risk and Policy Analysis* (Cambridge University Press, New York, NY, 1990).

21. A. C. Miller and T. R. Rice, "Discrete Approximations of Probability Distributions," Management Science **29** (3), 352-362 (1983).

22. C. Mooney, A. I. Mushlin, and C. E. Phelps, "Targeting Assessments of Magnetic-Resonance-Imaging in Suspected Multiple-Sclerosis," Medical Decision Making **10** (2), 77-94 (1990).

23. D. Heckerman, E. Horvitz, and B. Middleton, "An Approximate Nonmyopic Computation for Value of Information," IEEE Transactions on Pattern Analysis and Machine Intelligence **15** (3), 292-298 (1993).

24. A. Mehrez, Y. Yuan, and A. Gafni, "The Search for Information - a Patient Perspective on Multiple Opinions," European Journal of Operational Research **85** (2), 244-262 (1995).

25. D. K. Owens and R. F. Nease, "A normative analytic framework for development of practice guidelines for specific clinical populations," Medical Decision Making **17** (4), 409-426 (1997).

26. M. G. M. Hunink, K. M. Kuntz, K. E. Fleischmann, and T. J. Brady, "Noninvasive imaging for the diagnosis of coronary artery disease: Focusing the

development of new diagnostic technology," Annals of Internal Medicine **131** (9), 673-680 (1999).

27. K. Claxton, P. J. Neumann, S. Araki, and M. C. Weinstein, "Bayesian value-of-information analysis - An application to a policy model of Alzheimer's disease," International Journal of Technology Assessment in Health Care **17** (1), 38-55 (2001).

28. D. Meltzer, "Addressing uncertainty in medical cost-effectiveness analysis - Implications of expected utility maximization for methods to perform sensitivity analysis and the use of cost-effectiveness analysis to set priorities for medical research," Journal of Health Economics **20** (1), 109-129 (2001).

29. M. S. Thompson, "Decision-analytic determination of study size. The case of electronic fetal monitoring," Medical Decision Making. **1** (2), 165-79 (1981).

30. A. D. Paltiel and E. H. Kaplan, "The Epidemiologic and Economic Consequences of Aids Clinical- Trials," Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology **6** (2), 179-190 (1993).

31. K. Claxton and J. Posnett, "An economic approach to clinical trial design and research priority-setting," Health Economics **5** (6), 513-524 (1996).

32. J. Hornberger, "A cost-benefit analysis of a cardiovascular disease prevention trial, using folate supplementation as an example," American Journal of Public Health **88** (1), 61-67 (1998).

33. J. Hornberger and P. Eghtesady, "The cost-benefit of a randomized trial to a health care organization," Controlled Clinical Trials **19** (2), 198-211 (1998).

34. K. Claxton, "Bayesian approaches to the value of information: Implications for the regulation of new pharmaceutical," Health Economics **8** (3), 269-274 (1999a).

35. K. Claxton, "The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies," Journal of Health Economics **18** (3), 341-364 (1999b).

36. D. J. Cher and M. Maclure, "Use of randomized controlled trials in organizational decision making: A cost-minimization approach," American Journal of Managed Care **6** (8), 894-904 (2000).

37. K. Claxton and K. M. Thompson, "A dynamic programming approach to the efficient design of clinical trials," Journal of Health Economics **20** (5), 797-822 (2001).

38. D. W. North and M. W. Merkhofer, "A methodology for analyzing emission control strategies," Computers & Operations Research **3** (2-3), 185-207 (1976).

39. A. M. Finkel and J. S. Evans, "Evaluating the Benefits of Uncertainty Reduction in Environmental-Health Risk Management," JAPCA-the International Journal of Air Pollution Control and Hazardous Waste Management **37** (10), 1164-1171 (1987).

40. J. S. Evans, N. C. Hawkins, and J. D. Graham, "The Value of Monitoring for Radon in the Home - a Decision- Analysis," JAPCA-the International Journal of Air Pollution Control and Hazardous Waste Management **38** (11), 1380-1385 (1988).

41. H. P. Chao, S. C. Peck, and Y. S. Wan, "Managing Uncertainty - the Tropospheric Ozone Challenge," Risk Analysis **14** (4), 465-475 (1994).

42. M. E. Dakins, J. E. Toll, and M. J. Small, "Risk-Based Environmental Remediation - Decision Framework and Role of Uncertainty," Environmental Toxicology and Chemistry **13** (12), 1907-1915 (1994).

43. M. E. Dakins, J. E. Toll, M. J. Small, and K. P. Brand, "Risk-based environmental remediation: Bayesian Monte Carlo analysis and the expected value of sample information," Risk Analysis **16** (1), 67-79 (1996).

44. K. M. Thompson and J. S. Evans, "The value of improved national exposure information for perchloroethylene (Perc): A case study for dry cleaners," Risk Analysis **17** (2), 253-271 (1997).

45. C. Y. Lin, A. Gelman, P. N. Price, and D. H. Krantz, "Analysis of local decisions using hierarchical modeling, applied to home radon measurement and remediation," Statistical Science **14** (3), 305-328 (1999).

46. S. M. Bartell, R. A. Ponce, T. K. Takaro, R. O. Zerbe, G. S. Omenn, and E. M. Faustman, "Risk estimation and value-of-information analysis for three proposed genetic screening programs for chronic beryllium disease prevention," Risk Analysis **20** (1), 87-99 (2000).

47. L. B. Lave and G. S. Omenn, "Cost-Effectiveness of Short-Term Tests for Carcinogenicity," Nature **324** (6092), 29-34 (1986).

48. L. B. Lave and G. S. Omenn, "Screening Toxic-Chemicals - How Accurate Must Tests Be," Journal of the American College of Toxicology **7** (5), 565-574 (1988).

49. L. B. Lave, F. K. Ennever, H. S. Rosenkranz, and G. S. Omenn, "Information Value of the Rodent Bioassay," Nature **336** (6200), 631-633 (1988).

50. L. J. Olson, "The Search for a Safe Environment - the Economics of Screening and Regulating Environmental Hazards," Journal of Environmental Economics and Management **19** (1), 1-18 (1990).

51. A. C. Taylor, J. S. Evans, and T. E. McKone, "The Value of Animal Test Information in Environmental-Control Decisions," Risk Analysis **13** (4), 403-412 (1993).

52. G. S. Omenn, S. Stuebbe, and L. B. Lave, "Predictions of Rodent Carcinogenicity Testing Results - Interpretation in Light of the Lave-Omenn Value-of-Information Model," Molecular Carcinogenesis **14** (1), 37-45 (1995).

53. J. Massmann and R. A. Freeze, "Groundwater Contamination from Waste Management Sites - the Interaction between Risk-Based Engineering Design and Regulatory Policy .2. Results," Water Resources Research **23** (2), 368-380 (1987).

54. E. G. Reichard and J. S. Evans, "Assessing the Value of Hydrogeologic Information for Risk-Based Remedial Action Decisions," Water Resources Research **25** (7), 1451-1460 (1989).

55. T. Tucciarelli and G. Pinder, "Optimal Data Acquisition Strategy for the Development of a Transport Model for Groundwater Remediation," Water Resources Research **27** (4), 577-588 (1991).

56. R. A. Freeze, B. James, J. Massmann, T. Sperling, and L. Smith, "Hydrogeological Decision-Analysis .4. The Concept of Data Worth and Its Use in the Development of Site Investigation Strategies," Ground Water **30** (4), 574-588 (1992).

57. J. M. Wagner, U. Shamir, and H. R. Nemati, "Groundwater Quality Management under Uncertainty - Stochastic- Programming Approaches and the Value of Information," Water Resources Research **28** (5), 1233-1246 (1992).

58. B. R. James and R. A. Freeze, "The Worth of Data in Predicting Aquitard Continuity in Hydrogeological Design," Water Resources Research **29** (7), 2049-2065 (1993).

59. B. R. James and S. M. Gorelick, "When Enough Is Enough - the Worth of Monitoring Data in Aquifer Remediation Design," Water Resources Research **30** (12), 3499-3513 (1994).

60. B. R. James, J. P. Gwo, and L. Toran, "Risk-cost decision framework for aquifer remediation design," Journal of Water Resources Planning and Management-Asce **122** (6), 414-420 (1996).

61. B. J. Wagner, "Evaluating data worth for ground-water management under uncertainty," Journal of Water Resources Planning and Management-Asce **125** (5), 281-288 (1999).

62. C. E. Phelps and A. I. Mushlin, "On the (near) equivalence of cost-effectiveness and cost-benefit analyses," International Journal of Technology Assessment in Health Care. **7** (1), 12-21 (1991).

63. M. C. Weinstein, J. E. Siegel, M. R. Gold, M. S. Kamlet, and L. B. Russell, "Recommendations of the panel on cost-effectiveness in health and medicine," Jama-Journal of the American Medical Association **276** (15), 1253-1258 (1996).

Figure 1.1: Cumulative number of VOI applications over time

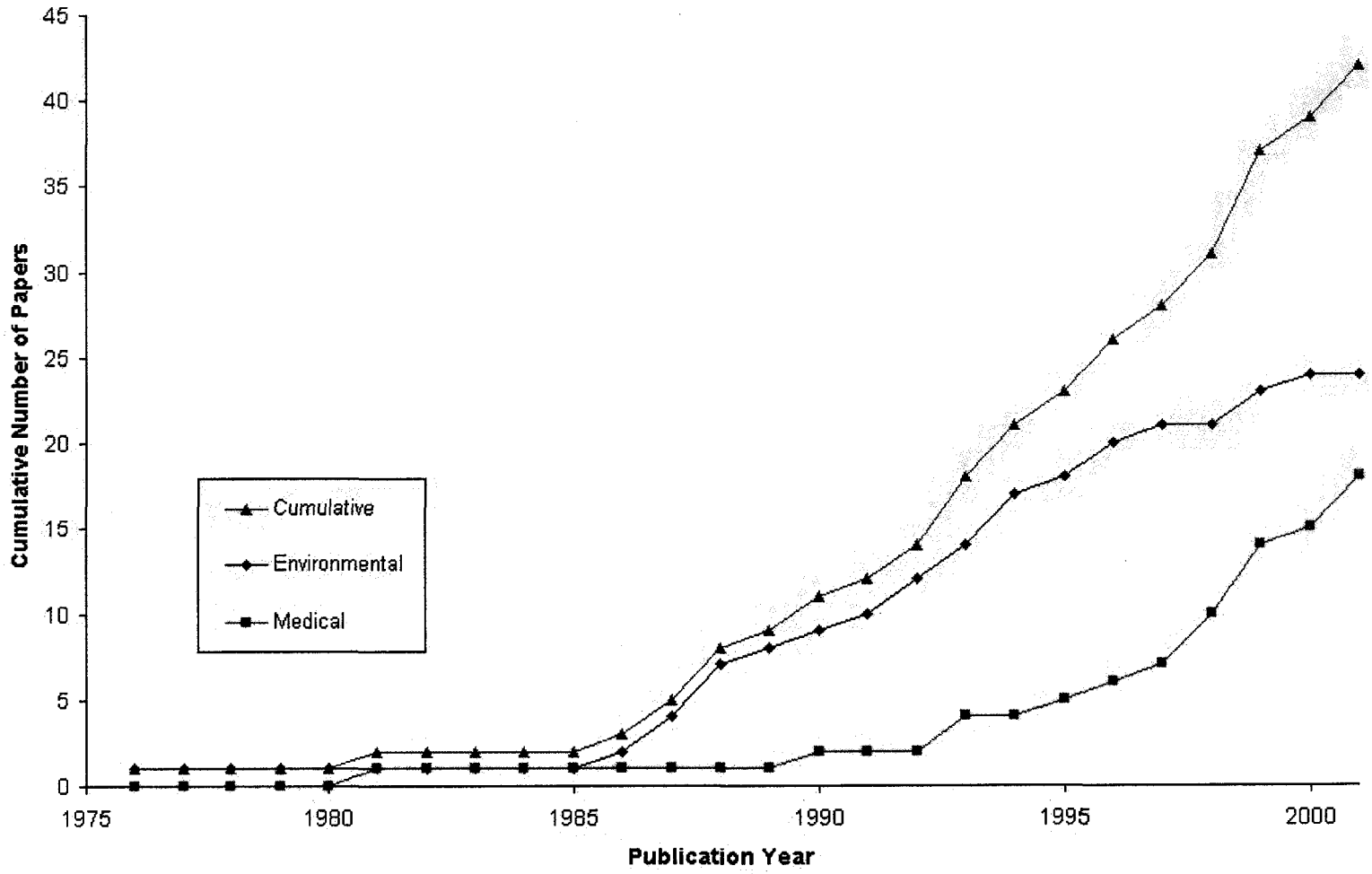

Table 1.1: Journals that published VOI applications

The American Journal of Managed Care (1)

American Journal of Public Health (1)

Annals of Internal Medicine (1)

Computers & Operations Research (1)

Controlled Clinical Trials (1)

Environmental Toxicology and Chemistry (1)

European Journal of Operations Research (1)

Ground Water (1)

Health Economics (3)

IEEE Transactions on Pattern Analysis and Machine Intelligence (1)

International Journal of Technology Assessment in Health Care (1)

Journal of Acquired Immune Deficiency Syndromes (1)

Journal of Environmental Economics and Management (1)

Journal of Health Economics (3)

Journal of the Air Pollution Control Association (2)

Journal of the American College of Toxicology (1)

Journal of Water Resources Planning and Management (2)

Medical Decision Making (4)

Molecular Carcinogenesis (1)

Nature (2)

Risk Analysis (5)

Statistical Science (1)

Water Resources Research (6)

Note: Number of papers found in each journal in parentheses

Table 1.2: Summary of papers in VOILA database by topic area

	Actions	Info Col	Unc In	EVPI	EVSI	EVPXI	EVSXI	Solution	VOILA	Outside	Orig
General Medical Care											
Mooney et al.[22]	4	2	1	x	x			Disc			
Heckerman et al.[23]	2	2	1		x			Disc			x
Mehrez et al.[24]	2	∞	1	x	x			Closed			x
Owens and Nease[25]	2	2	1		x			Disc			x
Felli and Hazen[16]	3	0	6	x		x		Simul	x		x
Felli and Hazen[16]	2	0	7	x		x		Simul	-	-	-
Felli and Hazen[16]	2	0	9	x		x		Simul	-	-	-
Felli and Hazen[17]	4	0	10	x		x		Simul	x		x
Hunink et al.[26]	2	5	1		x			Disc			
Claxton et al.[27]	2	0	8	x		x		Simul	x	x	x
Meltzer[28]	2	2	1	x	x			Disc	x	x	x
Clinical Trials											
Thompson[29]	2	∞	2	x	x			D Con			x
Paltiel and Kaplan[30]	2	4	1	x	x			Indet			
Claxton and Posnett[31]	2	∞	1	x	x			Closed			x
Hornberger[32]	2	∞	2	x	x			Indet	x		
Hornberger and Eghtesady[33]	2	∞	2	x	x			D Con			x
Claxton[34]	2	∞	1	x	x			Closed	x	x	x
Claxton[35]	2	∞	1	x	x			Closed	x		x
Cher and Maclure[36]	2	∞	1	x	x			Simul	x		x
Claxton and Thompson[37]	5	∞	1		x			Closed	x	x	x
General Environmental Health											
North and Merkhofer[38]	4	0	2	x				Indet			x
Finkel and Evans[39]	3	0	2	x		x		D Con			x
Evans et al.[40]	5	2	2				x	D Con	x		x
Chao et al.[41]	∞	2	3		x			D Con			

	Actions	Info Col	Unc In	EVPI	EVSI	EVPXI	EVSXI	Solution	VOILA	Outside	Orig
Dakins et al.[42]	∞	0	6	x				Simul	x	x	x
Dakins et al.[43]	∞	4	1		x			Simul	x	x	
Thompson and Evans[44]	11	0	14	x		x		Simul	x	x	
Lin et al.[45]	2	4	1		x			Simul	x		
Bartell et al.[46]	2	4	7				x	Simul	x		x
Toxicology											
Lave and Omenn[47]	2	2	1		x			Disc			
Lave and Omenn[48]	2	2	1		x			Disc	x		
Lave et al.[49]	2	2	1		x			Disc	x		
Olson[50]	2	3	1		x			Disc	x		
Taylor et al.[51]	2	3	1	x	x			D Con	x	x	x
Omenn et al.[52]	2	2	1		x			Disc	x		
Water Contamination											
Massmann and Freeze[53]	2	3	1		x			Closed			
Reichard and Evans[54]	2	4	2	x		x	x	D Con	x	x	x
Tucciarelli and Pinder[55]	∞	4	1		x			Mom	x		
Freeze et al.[56]	2	2	1	x	x			Disc	x		
Wagner et al.[57]	∞	0	1	x				Simul			
James and Freeze[58]	2	∞	1	x	x			Simul	x		
James and Gorelick[59]	∞	∞	3	x	x			Simul	x		
James et al.[60]	3	0	13	x				Simul	x		
Wagner[61]	∞	∞	6	x	x			Mom	x		

Note: Act = number of actions; Info = number of information collection strategies; Unc = number of uncertain inputs; EVPI = calculated EVPI; EVSI = calculated EVSI; EVPXI = calculated EVPXI; EVSXI = calculated EVSXI; Disc = discrete; Closed = closed form; Mom = method of moments; D Con = discretized continuous distribution; Simul = simulation; Indet = solution method indeterminate; VOILA = cited a paper in the VOILA database; Outside = cited a VOILA paper outside their topic area; Orig = cited one of the original decision analysis texts by Howard or Raiffa and colleagues

Table 1.3: Attributes of VOI analyses by topic area (count of applications)

	Med	Trial	EH	Water	Tox	All	
Total Applications	11	9	9	9	6	44	-
Terminology							
"VOI" term in abstract or key words	7	3	6	4	3	23	52%
"VOI" used in text	9	7	8	5	5	34	77%
Motivation for decision							
Societal policy	1	7	8	1	6	23	52%
Corporate decision	1	2	0	8	0	11	25%
Individual decision	9	0	2	0	0	11	25%
Perspectives							
Societal perspective	5	7	8	1	6	27	61%
Corporate perspective	1	2	0	8	0	11	25%
Individual perspective	5	0	2	0	0	7	16%
Decision Analytic Framework							
Cost-benefit or benefit-cost analysis	1	2	6	1	6	16	36%
Cost-effectiveness analysis	6	6	0	0	0	12	27%
Other objective function	4	1	3	8	0	16	36%
Valuation							
Year dollar reported	3	1	4	2	1	11	25%
Non-zero discount rate reported	3	6	5	5	1	20	45%
Time horizon for useful life of info	2	7	0	6	1	16	36%
Aggregate for total affected population	2	8	0	1	1	12	27%
Lump sum consequence of outcome	1	0	1	0	4	6	14%
Value per effectiveness	6	6	0	0	0	12	27%
Premature death averted	0	2	5	1	2	10	23%
Morbidity prevented	0	1	2	0	0	3	7%
Ecological damage	0	0	1	0	0	1	2%
Cost of control/treatment	6	9	9	9	2	35	80%
Cost of information collection	4	9	3	6	6	28	64%

	Med	Trial	EH	Water	Tox	All	
Uncertainty and Variability							
Binary uncertain input	5	0	1	2	5	13	30%
Only one uncertain input	6	6	2	5	6	25	57%
Parametric variable input	0	0	0	5	0	5	11%
Includes subgroups	2	0	4	2	0	8	18%
Distribution							
Discrete distribution	5	0	1	2	5	13	30%
Empirical distribution	1	1	1	0	0	3	7%
Parametric distribution	6	9	9	6	1	31	70%
Data Source							
Only Hypothetical	3	6	2	5	0	16	36%
Empirical Data	7	3	6	3	6	25	57%
Expert Judgment	2	0	1	0	0	3	7%
Model Output	0	0	2	2	0	4	9%
Analysis							
Threshold Analysis; VOI>0	1	0	1	1	3	6	14%
Maximize VOI	0	9	0	3	0	12	27%
EVPI "Overestimate"	2	4	3	6	0	15	34%
VOI "Underestimate"	0	0	2	1	0	3	7%

Table 1.4: Base case value of quality adjusted life years (QALYs)

Reference	Year Dollar	Value per QALY	2002 Dollars
Mooney et al.[22]	1987	$25,000	$35,000
Owens and Nease[25]	1993	$50,000	$62,000
Hornberger and Eghtesady[33]	NR	$50,000	$55,000
Hornberger[32]	NR	$50,000	$55,000
Hunink et al.[26]	1996	$75,000	$86,000
Meltzer[28]	NR	$100,000	$101,000
Claxton et al.[27]	NR	$50,000	$51,000

Table 1.5: Base case value of life

Reference	Year Dollar	Value per life	2002 Dollars
North and Merkhofer[38]	NR	$30,000	$94,000
Thompson[29]	1981	$175,000	$346,000
Finkel and Evans[39]	NR	$1,000,000	$1,600,000
Evans et al.[40]	NR	$3,000,000	$4,600,000
Reichard and Evans[54]	NR	$1,000,000	$1,500,000
Olson[50]	1986	$2,000,000	$3,300,000
Taylor et al.[51]	NR	$10,000,000	$12,000,000
Thompson and Evans[44]	1989	$3,000,000	$4,400,000

Appendix

Information collected about each application

Background
- Title
- Authors
- Journal
- Year of publication
- Abstract
- Key words
- Cited references
- Citing references
- Topic area

Terminology
- Were the terms "information value", "value of information", "value of perfect information", or "value of sample information" in abstract or key words?
- In the text?

Motivation for decision
- Was the decision a societal policy?
- Corporate decision?
- Individual decision?

Perspectives
- Did the analysis take a societal perspective?
- Corporate perspective?
- Individual perspective?

Decision Variables
- Was the decision an optimization problem (i.e., use a continuous decision variable)?
- Number of discrete actions if not optimized (including do nothing)
- Was the information collection strategy an optimization problem?
- Number of discrete information collection strategies if not optimized (including collect no additional information)

Decision Analytic Framework
- Did the analysis use cost-benefit or benefit-cost analysis?
- Did the analysis use cost-effectiveness analysis?
- Or did they use a different framework?

Valuation
- Year of currency

- Discount rate
- Time horizon for the useful life of information (i.e., when will the information become obsolete?)
- Total number of people affected by the information
- Crude, lump sum number to value the consequences of outcomes
- Value per effectiveness unit
- Value of premature death averted (e.g., loss of life, reduction in life years)
- Value of morbidity prevented (e.g., reduction in quality of life, pain and suffering)
- Value of ecological damage prevented
- Cost of control pollution/administering treatment
- Cost of information collection

Uncertainty and Variability
- Was the uncertain input binary (e.g., diseased or not, carcinogenic or not)?
- Number of uncertain inputs included in the VOI analysis
- Did the analysis contain a parametric variable input (e.g., spatially variable hydrogeologic input)?
- Include analysis by subgroups to account for variability?

Distribution
- Did the analysis characterize the uncertainty with a discrete distribution?
- An empirical distribution (i.e., discrete values observed in an empirical study)?
- A parametric distribution (e.g., normal, lognormal, uniform)?
- Some other distribution?

Data Source
- Did the analysis use hypothetical or synthetic data to characterize uncertainty?
- Empirical data?
- Formal expert judgment elicitation?
- Output of a separate model?

Analysis
- Did the analysis include components of EVPI? EVPXI? EVSI? EVSXI?
- Was the analysis framed as a threshold analysis (i.e., conditions which make VOI positive)?
- Was it framed as a maximization of VOI?
- Was EVPI characterized as an overestimate or an upper bound or maximum willingness to pay for additional information?
- Was EVPI or EVSI characterized as an underestimate of true societal willingness to pay since information collection could be useful in other decision contexts, or may yield additional benefits not included in the analysis?

Solution Strategy
- Were all of the probabilities discrete (i.e., required only simple arithmetic or discrete tree)?

- Was the problem solved exactly using closed form solution (e.g., used conjugate priors)?
- Method of moments approximation?
- Numerically integrate values or otherwise discretize continuous distributions?
- Monte Carlo simulation method?
- Or was the method indeterminate from the information given in the paper?

Chapter 2: Value of Information Analysis in Environmental Health Risk Management - Past, Present, and Future

Fumie Yokota and Kimberly M. Thompson

To be published in *Risk Analysis*

Abstract

Experts agree that Value of Information (VOI) analyses can be useful in real risk management decisions, however, applications in environmental health risk management (EHRM) have largely been demonstrative thus far because of the complexity in modeling and solving VOI problems. Lack of VOI applications in actual management decisions is partly due to the inherent complexities in modeling the underlying probabilistic risk assessment. The main barrier, however, appears to be the complexity of solving value of information analyses, since even the simplest problems with continuous probability distributions can be difficult to solve. Currently, simulation allows analysts to solve more complex and realistic problems that may be useful in real decision making contexts. Nonetheless, many analytical challenges remain that inhibit greater use of VOI techniques, including issues related to modeling decisions, valuing outcomes, and characterizing uncertain and variable model inputs. The comprehensive review of methods for modeling and solving VOI problems and the critical review of applications related to EHRM in this paper provides the first synthesis of important methodological advances in the field. The insights gained from the review of methods and applications in the EHRM literature will provide risk analysts and decision scientists with some guidance on how to structure and solve VOI problems focused on evaluating opportunities to collect better information to improve environmental health risk management decisions.

Key words: value of information, Bayesian decision theory, environmental health, risk analysis, risk management

1. Introduction

Value of information (VOI) analysis evaluates the benefit of collecting additional information to reduce or eliminate uncertainty in a specific decision making context. As noted in one of the earliest published VOI applications, "no theory that involves just the probabilities of outcomes without considering their consequences could possibly be adequate in describing the importance of uncertainty to a decision maker."[1:26] VOI analysis makes explicit any expected potential losses from errors in decision making due to uncertainty and identifies the "best" information collection strategy as one that leads to the greatest net benefit to the decision maker (DM). The recent Presidential/Congressional Commission on Risk Assessment and Risk Management (1997), noted that "when stakes in a decision are large and the uncertainties complex, risk managers or their technical staffs may find it useful to experiment with formal value-of-information tools."[2:92] Although methods for modeling and solving VOI analyses were introduced in some of the earliest publications on decision analysis decades ago[1,3-7] and the potential utility of applying the framework to environmental health risk management (EHRM) is widely recognized, unlike other decision analytic methods such as cost-benefit analysis and cost-effectiveness analysis very few VOI applications in EHRM exist. Moreover, recent analysis of VOI applications shows the tendency of papers to focus on demonstrating the usefulness of the VOI approach rather than applications to actual management decisions.[8]

The lack of VOI applications in actual management decisions appears to arise in part from the inherent complexities in modeling the underlying probabilistic risk

assessment and decision analysis. The analyst must model all relevant sets of actions and information collection strategies available to the DM, capture all significant consequences of each action given all possible states of the world, value those outcomes in a common metric, and characterize important uncertainty, variability, and the accuracy of information to be collected by fitting probability distributions to available information. In addition, for VOI calculations analysts cannot "conservatively" model a VOI problem to bias VOI towards a low value since no general monotonic relationships exist between VOI and action flexibility (i.e., increasing actions available to the DM), level of the DM's risk aversion, the DM's wealth, or the level of initial uncertainty in the prior distribution.[9]

The "experimentation" to date with the use of VOI analysis in EHRM decisions suggests that the complexity of models makes solving many VOI problems difficult. In particular, the solution of even the simplest VOI problem with continuous probability distributions can be computationally difficult.[6:60] While many texts exist to guide analysts in finding closed form solution to models with uncertainty expressed as set of discrete value-probability pairs or the small set of special continuous probability distributions with conjugate priors that allow analytical derivation of likelihood functions,[1,3-6,10] VOI analyses that inform real risk management decisions generally do not exactly fit into these simple forms and are nearly impossible to solve without numerical approximation methods.

With the increasing evolution of simulation strategies, examples of fairly complex VOI problems now appear in the literature. However, many analytical challenges remain and Ron Howard's prediction in 1967 still rings true: "[I]t is inevitable that in the future

both technical and managerial decision-makers will employ formal logical methods in decision-making. The transition will probably be painful."[6:60]

Currently, no analysis exists that demonstrates the impact of the choice of computational strategy on the accuracy of the approximation or how to correctly set up VOI analysis using methods such as simulation. The comprehensive review of methods for modeling and solving VOI problems and the critical review applications related to EHRM in this paper provides the first synthesis of important methodological advances in the field. In section 2 we define different types of VOI analysis and identify important issues related to modeling the VOI problem. In section 3 we demonstrate methods for solving VOI problems and compare the implications of different methods. Section 4 provides a critical review of sixteen VOI applications in EHRM[11-26] and shows how advances in computing tools have allowed analysis of problems with greater complexity. Section 5 identifies remaining analytical challenges including issues related to modeling decisions, valuing outcomes, and characterizing uncertain and variable model inputs that inhibit greater use of VOI techniques. The insights gained from the review of methods and applications in the EHRM literature lead to conclusions and recommendations in section 6 that provide risk analysts and decision scientists with some guidance on how to structure and solve VOI problems focused on evaluating opportunities to collect better information to improve environmental health risk management decisions.

2. Modeling Value of Information Analyses

The expected value of perfect information (EVPI) represents the value of completely eliminating uncertainty (i.e., collecting information with perfect accuracy). For an expected utility maximizer, EVPI about an uncertain input s is defined as:

$$EVPI = \int_{s \in S} \left[\max_{a \in A} u(a,s) \right] f(s)\,ds - \max_{a \in A} \left[\int_{s \in S} u(a,s) f(s)\,ds \right] \quad (1)$$

where $f(s)$ is the probability distribution representing prior belief about the likelihood of s. The first term represents the weighted average of the utility associated with taking the optimal action for all possible values of s over the prior belief about the likelihood of s. The second term represents the expected utility from taking an action that yields the highest expected utility.

When the DM faces multiple sources of uncertainty, the expected value of perfect X information (EVPXI) (where X represents is a particular uncertain model input) can be a useful measure for determining the relative importance of resolving uncertainty between inputs. For example, if a DM faces two uncertain inputs x and y, EVPI about x (called EVPXI) is:

$$EVPXI = \int_{x \in X} \left[\max_{a \in A} \int_{y \in Y} u(a,x,y) f(y \mid x)\,dy \right] f(x)\,dx - \max_{a \in A} \left[\int_{y \in Y} \int_{x \in X} u(a,x,y) f(x,y)\,dx\,dy \right] \quad (2)$$

where $u(a,x,y)$ is the utility of the DM, $f(y|x)$ is the prior conditional probability of y given x, $f(x)$ is the prior probability of x, and $f(x,y)$ is the prior joint distribution of x and y. EVPXI is the difference between the expected utility from taking the optimal action based on the revelation of the exact value of one uncertain input, x, and the expected

utility from the optimal decision given only the prior information. EVPXI has a peculiar non-additive property such that the sum of EVPXI from all sources of uncertainty do not necessarily sum to the total EVPI for resolving all uncertainties simultaneously.[1,27,28]

Since obtaining perfect information is nearly impossible, the more relevant measure of information value in decision making is the expected value of sample information (EVSI) or expected value of imperfect information. Calculating EVSI requires a preposterior analysis, so called since a decision must be made before the information is collected and the sample outcome is known. It requires a Bayesian updating of the probability of s for all possible sample information, t. The posterior probability of s given observation t, is defined as:

$$p(s|t) = \frac{f(s)\,g(t|s)}{h(t)} \tag{3}$$

where $g(t|s)$ is the likelihood function of observing t given a state of the world s, and $h(t)$ is the predictive density of t:

$$h(t) = \int_{s \in S} f(s)\,g(t|s)\,ds \tag{4}$$

The value of reducing but not eliminating uncertainty is:

$$EVSI = \int_{t \in T} \max_{a \in A} \left[\int_{s \in S} u(a,s)\,p(s|t)\,ds \right] h(t)\,dt - \max_{a \in A} \left[\int_{s \in S} u(a,s)\,f(s)\,ds \right] \tag{5}$$

EVSI is the difference between the expected utility of taking the optimal action based on the posterior probability of s given experimental information t, and the expected utility from taking the optimal decision given only the prior information about s. Without approximation methods, EVSI analyses would be nearly impossible since predictive density of the information sampled (equation 4) does not have a closed form solution

except for uncertainty expressed as a set of discrete probabilities or for select model structures such as likelihood functions with conjugate priors. In comparison, EVPI is a simpler calculation than the EVSI and may serve as a useful theoretical upper bound for the value of additional information for a particular decision context.

All VOI analyses require modeling a set of available actions, quantification and valuation of consequences, uncertainty and variability, and for EVSI, the accuracy of information collected. As discussed by Brand and Small,[29] within the context of the continuum from release of a substance into the environment to any ultimate health outcomes numerous opportunities may exist to obtain information and where these are obtained in the process may differentially impact the overall uncertainty about the final result. In any analysis, analysts can model the set of available actions and information collection strategies as a discrete set of actions or a continuous decision variable, and quantify all relevant consequences for each action, or value of the continuous decision variable, using an output value function that values monetary and non-monetary outcomes using a common metric, which is typically monetary in the context of VOI. The functional form and constraints must capture the objectives and preferences of the DM, such as risk aversion and discounting. For societal decisions and for decisions that impact large organizations that manage a portfolio of risks, typically the assumptions of risk neutrality and expected value decision making are applied, but these are not required for VOI problems. What is required is complete specification of the objective as a mathematical function, and model inputs as discrete values or random variables represented by probability distributions.

Most difficult to model are the uncertainty and variability in the decision, two related but distinct concepts. As the National Research Council's Committee on Risk Assessment of Hazardous Air Pollutants stated: "uncertainty forces decision makers to judge how *probable* it is that risks will be overestimated or underestimated for every member of the exposed population, whereas variability forces them to cope with the *certainty* that different individuals will be subjected to risks both above and below any reference point one chooses."[30:237] An intervention that is based on an average value of risk for a population will be too stringent for some and not stringent enough for others in the population.[31] These two concepts must be treated separately in VOI analyses since, unlike uncertainty, true variability cannot be reduced with more information.

The input distributions can include a discrete set of value-probability pairs when the input values are discrete, a distribution function that is uniquely defined by a set of parameters, an empirical distribution function based on a data set of observed values or subjective judgments from experts.[32] To characterize a distribution parametrically, analysts can use a variety of techniques for fitting available empirical data, formal expert judgment elicitation, or output from a model.[32-34] The type of distribution used should be selected to reflect the underlying scientific processes that generate the events characterized,[32] and it is critical to use a distribution that appropriately considers the characterization of uncertainty and variability.[24,27] When there are multiple inputs, the dependence must be characterized in the joint distribution. Fortunately, in those cases where inputs are independent, the joint distribution is simply the product of the two marginal distributions, greatly simplifying the calculation of VOI. This does not mean, however, that solving a VOI problem is easy.

3. Solving Value of Information Analyses

3.1 Overview

While the simplest applications where the uncertainty is characterized with a discrete distribution can be solved with "pencil and paper" by rolling back the decision tree, for more complex models analysts can use off-the-shelf software using decision trees, or in many cases write their own code to solve large and complex problems since a discrete approximation strategy is exponential in computational effort. For a small number of carefully chosen models with continuous distributions, simple applications may have closed form solutions that yield exact values. In general, however, problems with continuous inputs are more complex and the analyst may need to use one of several numerical approximation methods.

One strategy is to approximate continuous inputs so that the problem can be solved as if the model inputs were discrete. Another strategy is to use simulation, which relies on randomly sampling input values to calculate an output value for each iteration and iterating enough times to create an output distribution that is a good approximation of the truth and is then used to make statistical inference.[27] The error in any approximation depends on how closely the input distributions used match the true distributions, which means that error decreases with increased computational effort where computational effort is a linear in the number of uncertain inputs.

We illustrate differences in solution strategies using a classic example from one of the first published illustrations of the VOI approach, an optimal bidding problem by Howard.[6] In this VOI problem, a company can make any bid to compete against

competitors to win a contract for a project. The DM for the company seeks to maximize profits and is assumed to be risk neutral. The company will only win the contract if its bid is lower than the lowest bid of the competitors, but since bids are submitted in secret, the company is uncertain about its competitors' bids. Given this formulation, the company will maximize the expected value of profit:

$$profit = (b - c)\, I(l > b) \tag{6}$$

where b is the company's bid, c is the uncertain cost of the project to the company, l is the lowest bid of the competitors, and $I(l > b)$ is an indicator variable that takes a value of 1 if the company wins the bid ($l > b$) and 0 otherwise. The two uncertain inputs are characterized by uniform distributions with a lower bound of 0 and an upper bound of 1 for the cost of the project, and a lower bound of 0 and an upper bound of 2 for the lowest bid of competitors. The analysis assumes that the project cost and lowest competitor's bid do not depend on the company's bid, and that the project cost and lowest bid are independent.

3.2 Solution Strategies

This VOI problem can be solved analytically as demonstrated by Howard.[6] Figure 2.1 represents a schematic for solving the expected value of profit under different information schemes. With only prior information, we evaluate the expected value of profit for each possible bid value and choose the bid that will maximize expected profit:

$$E\{profit \mid prior\} = \max_{b} \int_{l=0}^{2} \int_{c=0}^{1} (b - c)\, I(l > b)\, f(c)\, f(l)\, dc\, dl \tag{7}$$

For expected value of profit with perfect information about cost, we first evaluate the expected value of profit when lowest bid values are unknown, treating cost as a constant, and choose the bid that will maximize expected profit. We then take a weighted average of the expected profit over all possible values of cost:

$$E\{profit \mid cost\} = \int_{c=0}^{1} \left\{ \max_{b} \int_{l=0}^{2} (b-c) I(l>b) f(l) dl \right\} f(c) dc \tag{8}$$

Similarly, for perfect information about lowest bid we solve:

$$E\{profit \mid lowest\} = \int_{l=0}^{2} \left\{ \max_{b} \int_{c=0}^{1} (b-c) I(l>b) f(c) dc \right\} f(l) dl \tag{9}$$

Under perfect information about both lowest bid and cost, we choose the bid that will maximize profit then take a weighted average of the expected profit over all possible values of cost and lowest bid:

$$E\{profit \mid both\} = \int_{l=0}^{2} \int_{c=0}^{1} \max_{b} \{(b-c) I(l>b)\} f(c) f(l) dc\, dl \tag{10}$$

Given the nature of this problem, the first step in solving it using either discretization or simulation is discretization of the company's bid. We divide the continuous decision variable in increments of 0.01 from 0 to 1.99 for a total of 200 bid values (recognizing that a bid of 2 or greater is dominated since it will never beat the competitor's bid and therefore always yields a profit of 0).

3.2.1 Discretizing the input distributions

For the discretization approach, we demonstrate what happens if we divide the uniform distribution of each input into 10, 32, and 100 segments of equal probability, where we assign a value of the mean of each segment to generate the value-probability

pairs. Since the problem is now entirely discrete, the calculation of expected values is computationally straightforward and it collapses to the discrete versions of equations (7)-(10):

$$E\{profit \mid prior\} = \frac{1}{n^2} \max_{b_k} \left\{ \sum_{i=1}^{n} \sum_{j=1}^{n} (b_k - c_i) I(l_j > b_k) \right\} \tag{11}$$

$$E\{profit \mid cost\} = \frac{1}{n^2} \sum_{i=1}^{n} \max_{b_k} \left\{ \sum_{j=1}^{n} (b_k - c_i) I(l_j > b_k) \right\} \tag{12}$$

$$E\{profit \mid lowest\} = \frac{1}{n^2} \sum_{j=1}^{n} \max_{b_k} \left\{ \sum_{i=1}^{n} (b_k - c_i) I(l_j > b_k) \right\} \tag{13}$$

$$E\{profit \mid both\} = \frac{1}{n^2} \sum_{i=1}^{n} \sum_{j=1}^{n} \max_{b_k} \left\{ (b_k - c_i) I(l_j > b_k) \right\} \tag{14}$$

where b_k is the k-th bid value, n is the level of discretization , c_i is the i-th discretized value of cost, and l_j is the j-th discretized value of the lowest bid. A decision tree program can be used to find a solution, however, due to the large number of bids, we script a program in S-Plus to implement the following calculation (all of the S-Plus code is available from the authors) [NOTE TO REVIEWERS: WE PROVIDED IT IN APPENDIX FOR YOU AT THE END OF THE MANUSCRIPT]. With 200 bid values, the discretization approach requires the evaluation of $200n^2$ bid-cost-lowest bid scenarios for each equation (i.e., in this case 20,000, 204,800 and 20,000,000).

3.2.2 Simulating the input distributions

For the simulation approach, we use Latin Hypercube sampling in @Risk to generate 100 sets of 100 sample values for cost and lowest bid for a total 10,000 samples for each input. We then calculate output values using subsets of the samples (n = 100, n = 1,000, and n = 10,000) in S-Plus. Calculation of expected values differs for the

simulation approach since each of the n pairs of randomly sampled cost and lowest bid values yields a value of profit with probability equal to $1/n$. For the case with only prior information, we first evaluate the mean of profit for each sample given a particular bid value then choose the bid that will maximize expected profit:

$$E\{profit \mid prior\} = \max_{b_j} \frac{1}{n} \sum_{i=1}^{n} (b_j - c_i) I(l_i > b_j) \tag{15}$$

where b_j is the j-th bid value, c_i and l_i are values of cost and lowest bid from sample realization i. As the equation shows, the simulation approach requires the evaluation of $200n$ (i.e., 20,000, 2000,000, and 2,000,000) bid-cost-lowest bid scenarios. Similarly, the expected value of profit from perfect information about both cost and lowest bid is:

$$E\{profit \mid both\} = \frac{1}{n} \sum_{i=1}^{n} \max_{b_j} \{(b_j - c_i) I(l_i > b_j)\} \tag{16}$$

Finding the EVPXI is more complex since it requires taking one value as fixed and the other as uncertain. One solution is to use the discretization approach and solve equations (12) and (13) using the simulated input values as if they were discretized values, however, it requires the evaluation of $200n^2$ scenarios (i.e., 200,000,000 for 1,000 iterations). In general, if the input distributions are probabilistically independent and the output value function is linear in the other uncertain input, then we can substitute the expected value of the input in the output value function and solve for the EVPI of the other input as if there is only one uncertain input.[27,35] In the case of this optimal bid problem, we can manipulate equation (9), the analytical solution for the profit given lowest bid where cost is linear in profit, to get:

$$\int_{l=0}^{2}\left\{\max_{b}\int_{c=0}^{1}(b-c)I(l>b)f(c)\,dc\right\}f(l)\,dl=\int_{l=0}^{2}\left\{\max_{b}(b-E\{c\})I(l>b)\right\}f(l)\,dl \tag{17}$$

therefore, for the simulation approach, we evaluate the following:

$$E\{profit\,|\,lowest\}=\frac{1}{n}\sum_{i=1}^{n}\max_{b_j}\left\{(b_j-\bar{c})I(l_i>b_j)\right\} \tag{18}$$

where $\bar{c}$ is the mean of the sampled cost values:

$$\bar{c}=\frac{1}{n}\sum_{i=1}^{n}c_i \tag{19}$$

Analysts must be careful to consider the relationship of an uncertain input to the output value function since the expected value of a function of random variables is not necessarily equal to the function of the expected values of the random variables.[27] For the expected value from perfect information about cost, we cannot substitute expected value of lowest bid since it is not linear in profit. By manipulating equation (8) we get:

$$\int_{c=0}^{1}\left\{\max_{b}\int_{l=0}^{2}(b-c)I(l>b)f(l)\,dl\right\}f(c)\,dc=\int_{c=0}^{1}\left\{\max_{b}(b-c)E\{I(l>b)\}\right\}f(c)\,dc \tag{20}$$

where $E\{I(l>b)\}$ is the expected value of the indicator variable, or the probability that a particular bid will win. Therefore, for the simulation approach, we evaluate the following calculation:

$$E\{profit\,|\,cost\}=\frac{1}{n}\sum_{i=1}^{n}\max_{b_k}\left\{(b_j-c_i)\bar{I}_j\right\} \tag{21}$$

where $\bar{I}_j$ is the mean of the indicator variable for each bid:

$$\overline{I}_j = \frac{1}{n}\sum_{i}^{n} I\left(l_i > b_j\right) \tag{22}$$

Theses substitutions are not intuitive and have been conducted incorrectly by some. For example, in a medical decision making VOI problem with multiple independent uncertain inputs,[36] the authors calculate EVPXI as the difference between EVPI from resolving all uncertainties, and the EVPI from substituting the expected value of x:

$$EVPXI = EVPI - EVPI\,|\,\overline{x} \tag{23}$$

If there were only two uncertain inputs, x and y:

$$EVPI\,|\,\overline{x} = \int_{y\in Y}\left\{\max_{a\in A} u(a,\overline{x},y)\right\} f(y)\,dy - \max_{a\in A}\int_{y\in Y}\int_{x\in X} u(a,x,y)\,f(x)\,f(y)\,dxdy \tag{24}$$

however, as previously derived, the utility given expected value of x is equivalent to taking the expected value of the utility with respect to x,

$$u(a,\overline{x},y) = \int_{x\in X} u(a,x,y)\,f(x)\,dx \tag{25}$$

therefore, EVPI$|\overline{x}$ is EVPYI, which implies that:

$$EVPXI = EVPI - EVPYI \tag{26}$$

which means that the only way for equations (23) to be true is if EVPXI and EVPYI sum to the EVPI from resolving both uncertainty simultaneously, which is rarely true do to the non additive property of EVPXI explained in the previous section.

3.3 Computational Insights

Table 2.1 provides the exact analytical solutions, estimates obtained from discretization of uncertain inputs into 10, 32, and 100 value-probability pairs, and

estimates obtained from simulations using sample size of 100, 1,000, and 10,000. The analytical solution to the optimal bid problem shows that the expected value of perfect information about lowest bid (EVPLI) and of perfect information about cost (EVPCI) do not sum to the EVPI that occurs with simultaneous resolution both uncertainties. Moreover, the analysis shows that perfect information about lowest bid is much more valuable to the company than perfect information than cost.

As the level of discretization increases, the approximated values become closer to the actual analytical values. Similarly, when we estimate expected profits from one set of samples, as the number of samples increase, the estimates approach the analytic solution. The estimate from a sample size of 10,000 matches the analytical solution very closely. The table shows that given a level of computational burden, measured by the number of scenarios that must be evaluated, the simulation approach tends to yield estimates closer to the analytical solution per calculation for this relatively simple problem with just two uncertain inputs. Better accuracy for discretization may be achieved if we use more sophisticated techniques for discretizing the distributions such as Gaussian quadrature, but this adds another dimension of computational complexity requiring the inversion of a *n*x*n* matrix where *n* is the number of value-probability pairs.[37]

Unlike discretization that yields a single value, the stochastic nature of the simulation approach will lead to different estimates depending on the random seed for sampling. We demonstrate the impact of choice of computational strategy because for most VOI problems, there are no exact solutions to "check" the estimates from simulation. Therefore, it is important for the analyst to evaluate the robustness of the simulation result. For example, table 2.1 compares the mean, 95% confidence interval,

and range of estimates from ten sets of 100 samples and ten sets of 1,000 samples. As the number of samples in each set increases, the range of values and the 95% confidence intervals decrease and tend toward the analytical solution. This example also demonstrates that although the estimates vary, the ranges of values are closer to the analytical solution than the discretization approach with equivalent numbers of calculations.

4. Evolution of Methodology

4.1 Overview

We review in detail sixteen VOI analyses on EHRM[11-26] included in the VOILA database.[8] We exclude water resource related analyses in the database that focus on uncertainties related to hydrogeologic inputs rather than health outcomes. Table 2.2 summarizes the attributes of the sixteen VOI analyses included in this review grouped by solution method. For each paper the table indicates the type of VOI analysis, number of actions, number of information collection strategies, types of outcomes the analysis specifically valued, number of uncertain inputs, inclusion of analysis by subgroup to account for variability, types of probability distributions used, and whether the analysts used expert judgment or outputs of models as a source for input distributions. As the table shows, four analyses considered only the value of perfect information, while nine considered only the value from sample information, and three analyses considered both. Nine analyses considered only two action alternatives (do something or do nothing), while four considered multiple alternatives, and three considered optimizing the level of action given a continuous decision variable. Four analyses considered only the complete

resolution of uncertainty (i.e., perfect information), and did not evaluate the value of specific information collection schemes. Five analyses considered two information collection strategies (collect something or collect nothing), while seven compared multiple schemes.

Since VOI analyses in EHRM tend to focus on societal level policy decisions, they generally consider the impact of decisions from a societal perspective. There are, however, examples of modeling voluntary actions such as individual homeowner's decision to monitor for radon to assist in choosing a remediation strategy.[18,25] Almost all of the analyses use a cost-benefit framework with an objective of either maximizing net benefits or minimizing net costs.[11-21,24,26] However, three analyses minimize the cost of meeting a health based standard and do not explicitly value health related outcomes.[22,23,25] As indicated in table 2.2, in valuing consequences of interventions, five analyses used a lump sum estimate of all consequences, while eight explicitly valued a premature death averted, two valued the reduction in morbidity, and one valued ecological benefits. In addition, less than half used a non-zero discount rate to express the DM's time preference,[18-21,24-26] and less than a third reported whether all monetary values were adjusted to a common year dollar.[14,21-24]

The analyses varied greatly in complexity as measured by number of uncertain inputs of the model and incorporation of variability. As table 2.2 shows, half of the analyses included just one uncertain input, with the rest ranging from 2 to as many as 14. None used a distribution to characterize variability, but four used subgroups. Seven used discrete sets of value-probability pairs, while eleven used a variety of parametric distributions, and one used an empirical distribution. By and large these analyses relied

on fitting distributions to some mix of hypothetical and empirical data, however, one used formal expert judgment elicitation and three used outputs of a model as the source for characterizing uncertainty.

The group of discrete analyses represented very simple models that evaluated only two actions (do nothing or do something), and considered only one dichotomous uncertain input (carcinogenic or not). They used point estimates for prior uncertainty and likelihood of sample results based on hypothetical values and some empirical evidence. The remaining analyses tended to have larger set of actions, considered multiple sources of uncertainty, and primarily used parametric distributions to characterize uncertainty. The earlier applications (1976-1994) used the discretization of continuous inputs to solve the VOI problem, while more recent applications (1994-2000) shifted to simulation as the solution method. As the table shows, simulation applications tended to have more complicated decision models, considered more uncertain inputs, and used a wider range of distribution functions.

4.2 Modeling Decisions

The discrete analyses,[11-15] focused on EVSI from toxicological testing in determining the carcinogenicity of chemicals. Since these papers illustrated the VOI framework for a generic management decision rather than informing a specific real decision, they considered the very limited set of only two regulatory actions (do nothing or do something). These analyses assumed that a hypothetical, pre-set certain control decision would be followed if after testing the chemical was deemed carcinogenic. Most of these analyses consider only two information collection strategies. Two papers by

Lave and Omenn[11,12] considered the value of regulating chemicals based on the results of a short-term tests for carcinogenicity compared to allowing chemicals to go unregulated. Lave et al.[13] evaluated the benefit of conducting rodent bioassays to no testing. Olson,[14] however, compared acting on prior information to conducting a mutagenicity test and then evaluating whether to collect bioassay information or not. Omenn et al.[15] went a step further and compared 13 different approaches developed by various researchers that combine information on structure-activity relationships, short-term tests, sub-chronic rodent assays, and/or expert judgment for predicting the results of a lifetime rodent bioassay.

The analyses that discretized continuous uncertain inputs represent much more complex decision problems. The earliest two analyses focused on characterizing model uncertainty by measuring the value of perfect information, and they did not evaluate specific information collection schemes. North and Merkhofer[16] calculated the EVPI from resolving uncertainties in choosing four alternative strategies to control pollution emissions for three representative power plant types. Finkel and Evans[17] described a VOI framework for environmental management and calculated the EVPI and EVPXI for dose of a hypothetical risk management problem with three alternatives.

The next three analyses, on the other hand, evaluated specific information gathering strategies. Evans et al.[18] modeled homeowner's EVSXI from monitoring radon in the home in choosing one of five remediation strategies (where two of the five are always dominated and were not included in the final calculation). Reichard and Evans[19] considered the EVPI, EVPXI and EVSXI of four options for monitoring groundwater for arsenic in a decision to install point of use drinking water filtration

system or not. Taylor et al.[20], assessed the EVPI and EVSI of the animal bioassay's ability to determine magnitude of cancer causing potential rather than just whether a chemical is carcinogenic or not. The choice of actions used was simplistic (act or not), however, to provide general insights about the three strategies for collecting toxicological information: collect none, use only subchronic bioassay, or conduct additional long-term bioassay.

The last analysis in this group evaluated the benefit of a two-stage approach to pollution control, which allowed the incorporation of information collected from the first stage in the decision at the second stage. Chao et al.[21] calculated EVSI from waiting for more information to choose the optimal levels of control of both nitrogen oxides and volatile organic compounds to reduce tropospheric ozone. The level of emission reduction was divided into five levels for each pollutant (0%, 20%, 40%, 60%, 80%) for each stage, yielding 625 action scenarios.

The analyses that used simulation include two that considered only two action alternatives, and two others that do not consider specific information collections strategies. Dakins et al.[22,23] evaluated the value of resolving uncertainty about PCB contamination in fish to assist in choosing the optimal level of remediation of contaminated sediments in New Bedford Harbor, Massachusetts. Dakins et al.[22] evaluated EVPI for the model and Dakins et al.[23] conducted a preposterior analysis to evaluate the EVSI from sampling two, five, and ten randomly selected flounder from New Bedford Harbor. Thompson and Evans[24] calculated the EVPI and EVPXI from collecting national exposure information about perchloroethylene (perc) used in dry cleaning. Unlike other applications, this analysis compared regulating perc exposure at

three different levels of decision making: individual dry cleaning facilities, by particular dry cleaning machine category (defined by type and size), and by particular machine type, with several control options for each type of machine (a total of eleven).

The remaining two analyses, in contrast, focused on optimal information collection, and simple choice of action or no action. Lin et al.[25] evaluated the EVSI from measuring radon concentrations in private homes to assist in the decision to take remediation action or not, and compared four different policies for monitoring strategies at the national level. Bartell et al.[26] evaluated the EVSI from a screening program to prevent chronic beryllium disease (CBD) from occupational exposure. The analysis evaluates the value from resolving the uncertainty in the presence or absence of a genetic polymorphism that makes an individual susceptibility to CBD. They compared three different strategies for screening to doing nothing, where a "positive" screening result leads to an intervention that would lead to either early treatment of the disease or prevention of exposure to beryllium.

4.3 Modeling and Valuing Outcomes

Table 2.3 summarizes the health outcomes evaluated by the analyses and values used to calculate VOI. As the table shows, the discrete analyses used a simple cost-benefit framework, and did not have sophisticated measures of outcomes. Most of the discrete analyses[11-13,15] evaluated a lump sum for two consequences: a regulatory false positive is assumed to impose a net cost to society from unnecessarily regulating a non-carcinogen ($1 million), while a regulatory false negative is assumed to impose a net cost to society from not regulating a carcinogen ($10 million). The same baseline values are

used in all of these analyses although the earliest was published in 1986 and the latest in 1995. None of these analyses reported a discount rate or whether all monetary values were adjusted to a common year dollar. In contrast, Olson[14] calculated the number of cases of cancer from a hypothetical unregulated carcinogen and valued them at $2 million (1986 dollars) using a discount rate of zero.

The papers that discretized continuous uncertain inputs tended to develop much more sophisticated cost-benefit analyses and have more refined measures of outcomes. North and Merkhofer[16] identified and valued a variety of health endpoints from air pollution including premature death ($30,000), aggravation of heat and lung disease symptoms ($20/day), asthma attack ($10/case), a child's lower respiratory disease ($75/case), and chronic respiratory disease ($250/case). They also estimated the cost of ecological damage ($0.015 per pound of sulfur emitted), and esthetic effects ($0.034 per pound of sulfur emissions), but did not report whether all monetary values were adjusted to a common year dollar or a discount rate.

Four analyses[17-20] modeled dose-response and exposure to estimate the risk of developing cancer from various carcinogens and used a nominal value of life ranging from $1 million to $10 million (with an even wider range in sensitivity analysis). Since the earliest analysis had the smallest baseline value and the latest had the largest, the difference in real value is likely even greater, but we cannot calculate it exactly since none of these three analyses reported what year dollar the values represented. The discount rate in these analyses ranged from 3% to 5%. Chao et al.[21] did not specifically measure a health end point, but instead estimated a lump sum value for the impact of

ozone concentration. They estimated damage to health from ozone at $10 billion per year per ppm if peak ozone concentration exceeded 0.12 ppm (in 1989 dollars).

The analyses that used simulation as a solution strategy took much more varied approaches to modeling outcomes. Two analyses[24,26] used a risk assessment approach to evaluate the net societal costs from health damages caused by exposure to perc and CBD, respectively. Thompson and Evans[24] valued each premature death from cancer at $3 million in 1989 dollars, with a range of $1 million to $10 million in sensitivity analyses. They used a consistent discount rate of 5% in the base case analysis to account for time preference. Bartell et al.[26] valued a case of CBD prevented using four different estimates ranging from a low estimate of $12,200 that considered only future medical costs averted discounted at 7%, to a high number of $16,300,000, which is a high estimate of the value of a statistical life ignoring disease latencies and discounting (no year dollar given).

Taking a slightly different approach, Lin et al.[25] modeled risks of cancer from radon exposure, but rather than use a specific value per life to drive the analysis, they used an action level as the benchmark assuming that above the set level of exposure remediation should occur. The action level was predetermined based on household composition, a household's risk preference, and WTP for risk reduction. The objective focused on minimizing total cost, which included residual risk after remediation. In the base case analysis, the authors chose an action level established by the U.S. EPA, an annual living area average concentration of 4 pCi/L. Assuming a household consisting of the average number of male and female smokers and never smokers in the United States, the action level implied a value of $210,000 per life. They used a discount rate of 5% to

account for time preference, but did not report whether all monetary values were adjusted to a common year dollar.

In contrast the objective of Dakins et al.[22,23] focused on choosing an optimal level of dredging to minimize remediation costs while meeting a health-based standard for PCB concentration in fish set by the FDA. The analysis, which evaluated the cost of under remediation in 1985 dollars and use a 0% discount rate, assumed that the correct level of remediation will be known in the future and assumed no residual health risk if the standard is met. If insufficient remediation occurred, then additional remediation to meet the standard must be completed and would require additional penalties such as the fishery remaining closed for longer time and additional costs of remobilizing research and remediation efforts. This did not however account for health risks from sub-optimal dredging or any health risks that would exist either during or post-remediation. .

4.4 Characterization of Uncertainty and Variability

The discrete analyses represented simple models for the value of resolving uncertainty about a single dichotomous input – whether a chemical is carcinogenic or not – and used hypothetical point estimates of prior probability of carcinogenicity and point estimates for the likelihood of test results based on empirical data. The papers by Lave and Omenn[11,12] assumed a range of point estimates for the sensitivity and specificity of rodent bioassays in predicting human carcinogens. Lave et al.[13] assumed point estimates for both sensitivity and specificity based on empirical evidence for each type of testing. Olson[14] also used a hypothetical prior but disaggregated likelihood into the four categories of possible bioassay results established by the U.S. National Toxicology

Program (NTP), and assumed discrete probability values based on available empirical evidence. Omenn et al.[15] compared 13 approaches for predicting results of a life-time rodent bioassay (carcinogenic or not) developed through the Carcinogenic Prediction Challenge sponsored by the NTP. They used a hypothetical point estimate of prior probability and the sensitivity and specificity values implied by the strategies for 44 chemicals.

The analyses that used a discretization approach tended to include only a couple of continuous uncertain inputs, and used lognormal distributions for prior distributions and/or likelihood functions that allowed analytical solutions for the product of inputs and posterior distributions. Only a couple of analyses explicitly addressed variability. The EVPI analysis by North and Merkhofer[16] evaluated the value of simultaneously resolving two uncertainties in the model: how a unit of emission translates to ambient concentration and the total health cost per unit increase in suspended sulfate concentration, which were assumed to be independent in the analysis. The characterizations were based on the authors' subjective judgment on extreme values, which were modeled to represent the 5th and 95th percentile points on the cumulative probability distribution. They provided a sketch of the cumulative distribution for the ambient sulfate concentration increment and assumed a lognormal distribution for the total health cost. To account for variability in the total health cost on local population density and fuel burning technology, they solved the optimization problem for three types of power plants: an existing coal plant in a rural area, a new construction in a rural area, and an oil burning plant (originally designed for coal) in an urban east coast location.

Finkel and Evans[17] modeled uncertainty about the health risk from a contaminant as the product of two components: dose and exposure. They assumed a lognormal distribution for both components and consequently the uncertainty about risk was also lognormal. They used hypothetical parameter values to illustrate how EVPI varied with different prior beliefs about the uncertainty in risk. Evans et al.[18] used the approach established by Finkel and Evans[17] to characterize the uncertainty in exposure to radon in individual homes and its potency in causing cancer. They developed lognormal distributions for both components using formal expert judgment elicitation. The expert set parameter value for the prior distribution for exposure based on previously available monitoring information (e.g., regional monitoring data, monitoring in a neighbor's home), and accounted for variability in radon exposure by setting different parameter values based on region of the country and characteristic of the home. They used a lognormal distribution to characterize the likelihood of observing a given a radon measurement. A different expert was asked to develop parameters for a lognormal distribution of excess relative risk of cancer to the general population based on epidemiological data available for occupational exposure of radon to miners. They included additional variability in potential benefits from monitoring by analyzing the VOI to household of four representative demographic compositions.

Reichard and Evans[19] used a similar approach and include two uncertain inputs characterized by a lognormal distribution: the potency of arsenic in causing cancer and the exposure to arsenic in well water. They assumed a lognormal distribution for potency, and fit a multistage dose response model to epidemiological data to estimate the geometric standard deviation of potency. For exposure to arsenic, however, the authors

used simulation to propagate uncertainty in a hydrogeologic model with five uncertain inputs characterized by uniform distributions, but rather than use the output of the simulation to characterize the uncertainty in exposure they fit a lognormal distribution for use in subsequent analysis. They also used an empirically based likelihood function to characterize the error in concentration measurement.

Taylor et al.,[20] unlike the other analyses in this group, included only one uncertain input in their model: carcinogenic potency of a chemical. The prior distribution of potency was based on the results of the first 213 NTP mouse bioassays. Since only half of the chemicals were determined to have positive results, for the base case analysis, the distribution is characterized as the sum of a delta function at zero potency with a probability mass of 50%, and a lognormal distribution fit to the statistically significant test results and normalized so that the entire distribution integrates to unity. They modeled likelihood of test results as a Binomial distribution and created a matrix of values to solve for the values of the posterior distribution. Chao et al.[21] expressed uncertainty in current emission rates of nitrogen oxides and volatile organic compounds as uniform distributions, and uncertainty in the photochemical model expressed as a lognormal distribution. Distributions and parameter values were chosen by the authors to represent their judgment on the best available information. The analysis models information available after the first stage as a sampling outcome with a hypothetical point estimate for accuracy.

Analyses that use simulation as solution strategies tended to include a number of continuous uncertain inputs and used a variety of parametric distributions to characterize uncertainty. Two of the analyses explicitly included variability in the analysis. The

EVPI analysis in Dakins et al.[22] evaluated simultaneously resolving all six uncertain inputs in the model such as PCB concentration in the sediment, average water temperature, and growth rate of flounder. They described each input by a normal, triangle, or uniform distribution to reflect the best available information for New Bedford Harbor collected for a previous food chain model (input distributions listed in table 2 of Ref. 22). Dakins et al.[23] modeled the prior distribution for body burden by simulating 50 replications using the model established in Dakins et al.[22] The only uncertain input used in this analysis was the PCB body burden of flounder, although it was derived from 6 uncertain inputs in a previous analysis. They conducted a preposterior analysis to evaluate the EVSI from sampling two, five, and ten randomly selected flounder from New Bedford Harbor. They assumed that the likelihood of observing a particular set of body burden measurements was normally distributed given a true value of total body burden. For the case of sampling five flounders, they repeated the simulation five times with different random seeds to check the robustness of the calculation using simulation results, and are the only ones to report multiple simulation results in a publication.

Thompson and Evans[24] considered fourteen uncertain inputs such as potency of perc in causing cancer, fraction of inhaled perc metabolized, perc's lifetime in the atmosphere, and uncertainty in predictions of a Gaussian dispersion model. They characterized the inputs using lognormal, triangular, or uniform distributions to best reflect the empirical evidence (references are noted on the list of input distribution in table 4 of reference [24]. The authors also used an empirical distribution to characterize perc's potency developed for a previously published risk assessment. Two inputs, fraction of time spent at a dry cleaning facility by consumers and workers, were developed based

on informal discussions with local dry cleaners. They considered variability by modeling risks to four distinct populations: dry cleaning workers, families of workers, consumers of dry cleaning services, and the general public from ambient exposure. Unlike all of the other analyses that use simulation, this paper includes an EVPXI analysis to evaluate the relative importance of the different sources of uncertainty. In this case, the authors found that the individual EVPXIs sum to a number larger than the overall EVPI (could you infer that this would happen in the paper by Finkel and Evans?).

In the analysis by Lin et al.,[25] the sole uncertain input in the model was the concentration of radon. The prior distribution was characterized by a lognormal distribution based on a hierarchical linear regression model that fit county level explanatory variables to radon measurements, yielding parameter values that varied by county and housing type. Additionally, the authors accounted for variability in risk of cancer based on gender and smoking status. For the base case, the authors assumed that long term monitoring produces an unbiased, lognormally distributed estimate of concentration such that the posterior distribution of true concentration given the measurement would also distribution lognormally. One commentator applauded the analysis, however added "given the power of modern MCM techniques I was surprised that the model components...were essentially confined to normal distributions."[38]

Bartell et al.[26] evaluated resolving the uncertainty in the presence or absence of a genetic polymorphism that makes an individual susceptible to CBD using a probabilistic risk assessment. The model included seven uncertain inputs such as sensitivity and specificity of the genetic screening test, cost of testing, cost of genetic counseling, and risk reduction efficacy from interventions. These inputs were characterized by beta,

triangular and uniform distributions to reflect the analysts' best judgment of available information (input distributions listed in table 1 of reference [26] where they also note their level of confidence about the characterization). They used a point estimate for the prior prevalence of susceptible individuals, and this value is updated based on information collected from three screening strategies with uncertain sensitivity and specificity to estimate the posterior probability of genetic polymorphism.

5. Remaining Analytical Challenges

The VOI analyses in EHRM decisions to date represent primarily demonstrations of the usefulness of approaching a management problem using a VOI framework. While simulation appears to be allowing analysts to solve more complicated and realistic problems that may be useful in real decision making contexts, important barriers remain. These include the lack of guidance from EPA and others on criteria for standardizing EHRM risk and decision analyses, the lack of consensus on values to use for health outcomes, the lack of default probability distributions for frequently used inputs, and inexperience of risk managers and communicators with using probabilistic risk results.[27] In addition, it remains analytically challenging to model decisions that use all available information, deal with non-linear inputs, and include correlation in input distributions and dependence in information collected.

For the societal perspective, analysts need to evaluate all relevant decision contexts where information would be useful. VOI can inaccurately estimate the true societal value of perfect information if positive or negative externalities may arise from the information collection not explicitly modeled in the decision. For example,

toxicological information about one substance may be used for the specific regulatory decision about controlling that substance, but it may also be used in models to predict toxicity of substances with similar structures. While some analysts have discussed this issue, no progress has been made on developing strategies to deal with it in VOI analyses.

With respect to modeling, none of the previous analyses have addressed non-linearity in risk models. Though cancer risks are generally modeled as a linear function of dose, current procedures for non-cancer risk assessment require a modeling a threshold under which no detrimental effects will occur. As discussed previously, when there are inputs that are not linear in the output value function, EVPXI cannot be calculated with simulation using a simple substitution of expected value of that input.

Another challenge is how to value non-monetary outcomes. Though economists have attempted to calculate a societal value for averting premature morbidity and mortality,[39,40] no widely agreed value exists. Not surprisingly, the values analysts choose to use vary widely, which is problematic since the choice of value of life can dramatically impact the VOI results.[24] In addition, empirical evidence from both revealed preference and stated preference studies show that factors such as age, income, baseline mortality risk, and latency of the risk influence the value of statistical life (VSL), but only income shows a predictable, monotonic relationship.[41] Similarly, no consensus exists on what discount rate to use to reflect societal time preference, an important model input for decisions related to diseases that may have long latencies, and latency in cancer remains a very difficult factor to include in risk models.

Collecting additional information may lead to surprises that show some basic assumptions may be incorrect, such as observing input values outside the bounds of prior

belief in those cases where the model used overconfident priors.[42,43] Given very limited information, the uniform and triangle distributions are maximum entropy distributions and may provide the best fit to existing information. However, collecting information about the input may lead to observations of values outside the bounds of the uniform or triangle distribution. In addition, prior distributions based on expert judgment may be overly narrow due to tendency of both lay people and experts to be overconfident in their knowledge.[43] Therefore, choice of prior distribution based only on fitting distributions to observed data or expert judgment may discount "surprises" that can be of great value from information collection,[42,43] and may not be desirable from VOI standpoint.

None of the EHRM analyses include correlated uncertain input distributions or assess the impact of dependence in information collected. Modeling correlated input distributions requires developing joint distributions and conditional probability distributions for EVPXI analyses, which complicates the calculation but could have an important impact on VOI. For example, positive dependence among sources may significantly reduce the value of information. Previous research suggests "it might be important to seek out information sources that are believed not to be highly correlated with each other or with the prior information...trading some precision for reduced dependence can be advantageous."[44]

As the case of mandatory passenger side airbags in motor vehicles show, significant consequences derive from ignoring variability in a decision analysis.[45] In addition, since true variability cannot be reduced with more information, a distribution that combines uncertainty and variability is not appropriate for VOI analyses and analysts must use care to treat the uncertainty and variability appropriately in the context of the

desired characterization of risk.[46, Thompson, 1996 #118] For example, a decision where a risk manager seeks to control the total number of cases of a disease, the variability in the population can be collapsed into the uncertainty in the model and that distribution should represent the uncertainty about the mean (i.e., the standard error), not the standard deviation of individuals in the population.[32]

The review suggests that analysts may have not sufficiently dealt with the issue of potential errors in VOI analyses stemming from numerical approximation methods. Only one analysis, Dakins et al.,[23] reports multiple simulation results to show the robustness of the VOI estimate, although Thompson and Evans[24] reported results that represented the mean of 10 simulations of 10,000 iterations each. As computational capabilities of personal computers increase, even large simulations are becoming much faster and cheaper than ever before such that for many problems the slowest part of the process is the time required to set up the model, not the time required to run it, which is trivial by comparison.

6. Conclusion

Rigorous value of information analysis is not required for all opportunities to collect information to improve EHRM decisions. However, complex risk management decisions as well as efforts to characterize uncertainty in risk may greatly benefit from formal VOI analyses. The National Research Council's Committee on Risk Characterization stated that: "Risk characterization should be a decision-driven activity, directed towards informing choices and solving problems"[47:155] and recognizes that "value-of-information analysis can be of considerable use in the analytic-deliberative

process."[47:111] Our analysis shows how advances in computing tools have allowed analysts to tackle of problems with greater complexity, but "real" applications are still lacking.

In the field of clinical decision making, the U.S. Public Health Service convened in 1993 the Panel on Cost-Effectiveness in Health and Medicine with the goal of standardizing methods used to estimate cost-effectiveness of medical interventions to improve the quality of the analyses and make them more comparable.[48] However, similar efforts have not appeared in the field of environmental health. An EHRM equivalent to the panel on cost effectiveness might be very helpful to standardize analytical methods and reporting requirements for value of information analyses as the field continues to evolve.

As with all analyses, the most important question may be deciding when to take the step of performing a formal VOI analysis. While we believe that more such analyses will be justified as decisions become more complex, we believe that Howard may have captured this best:

> [O]ne of the arts of the decision analyst is the art of knowing how much and what kind of decision analysis to do. The degree of analysis can range from making simple lists to constructing giant interactive computer models. To be effective decision analysis must be "appropriate": the extent of the analysis must be suitable to the means and ends of the decision-maker.[49:22]

Part of making sure that the means and ends of the decision-maker are met depends on increased dialogue between risk assessors, risk managers, and decision analysts about the opportunities presented by formal VOI analysis, and this paper shows that the literature contains a number of examples that may help make the case.

References

1. R. A. Howard, "Information Value Theory," IEEE Transactions on Systems Science and Cybernetics **SSC2** (1), 22-26 (1966).

2. Commission on Risk Assessment and Risk Management, *Framework for Environmental Health Risk Assessment* (Presidential/Congressional Commission on Risk Assessment and Risk Management, Washington, DC, 1997).

3. H. Raiffa, *Decision Analysis: Introductory Lectures on Choices under Uncertainty* (Random House, New York, NY, 1968).

4. J. W. Pratt, H. Raiffa, and R. O. Schlaifer, *Introduction to Statistical Decision Theory* (MIT Press, Cambridge, MA, 1995). (Originally distributed in 1965 by McGraw-Hill in mimeograph form)

5. H. Raiffa and R. O. Schlaifer, *Applied Statistical Decision Theory* (Division of Research, Graduate School of Business Administration, Harvard University, Cambridge, MA, 1961).

6. R. A. Howard, "Value of Information Lotteries," IEEE Transactions on Systems Science and Cybernetics **SSC3** (1), 54-60 (1967).

7. R. A. Howard, "The Foundations of Decision Analysis," IEEE Transactions on Systems Science and Cybernetics **SSC-4** (3), 211-219 (1968).

8. F. Yokota and K. M. Thompson, "Value of Information Literature Analysis (VOILA): A Review of Applications in Health Risk Management," Unpublished Manuscript, 2002.

9. R. W. Hilton, "The Determinants of Information Value: Synthesizing Some General Results," Management Science **27** (1), 57-64 (1981).

10. R. T. Clemen, *Making Hard Decisions* (Duxbury Press, Pacific Grove, CA, 1996).

11. L. B. Lave and G. S. Omenn, "Cost-Effectiveness of Short-Term Tests for Carcinogenicity," Nature **324** (6092), 29-34 (1986).

12. L. B. Lave and G. S. Omenn, "Screening Toxic-Chemicals - How Accurate Must Tests Be," Journal of the American College of Toxicology **7** (5), 565-574 (1988).

13. L. B. Lave, F. K. Ennever, H. S. Rosenkranz, and G. S. Omenn, "Information Value of the Rodent Bioassay," Nature **336** (6200), 631-633 (1988).

14. L. J. Olson, "The Search for a Safe Environment - the Economics of Screening and Regulating Environmental Hazards," Journal of Environmental Economics and Management **19** (1), 1-18 (1990).

15. G. S. Omenn, S. Stuebbe, and L. B. Lave, "Predictions of Rodent Carcinogenicity Testing Results - Interpretation in Light of the Lave-Omenn Value-of-Information Model," Molecular Carcinogenesis **14** (1), 37-45 (1995).

16. D. W. North and M. W. Merkhofer, "A methodology for analyzing emission control strategies," Computers & Operations Research **3** (2-3), 185-207 (1976).

17. A. M. Finkel and J. S. Evans, "Evaluating the Benefits of Uncertainty Reduction in Environmental-Health Risk Management," JAPCA-the International Journal of Air Pollution Control and Hazardous Waste Management **37** (10), 1164-1171 (1987).

18. J. S. Evans, N. C. Hawkins, and J. D. Graham, "The Value of Monitoring for Radon in the Home - a Decision- Analysis," JAPCA-the International Journal of Air Pollution Control and Hazardous Waste Management **38** (11), 1380-1385 (1988).

19. E. G. Reichard and J. S. Evans, "Assessing the Value of Hydrogeologic Information for Risk-Based Remedial Action Decisions," Water Resources Research **25** (7), 1451-1460 (1989).

20. A. C. Taylor, J. S. Evans, and T. E. McKone, "The Value of Animal Test Information in Environmental-Control Decisions," Risk Analysis **13** (4), 403-412 (1993).

21. H. P. Chao, S. C. Peck, and Y. S. Wan, "Managing Uncertainty - the Tropospheric Ozone Challenge," Risk Analysis **14** (4), 465-475 (1994).

22. M. E. Dakins, J. E. Toll, and M. J. Small, "Risk-Based Environmental Remediation - Decision Framework and Role of Uncertainty," Environmental Toxicology and Chemistry **13** (12), 1907-1915 (1994).

23. M. E. Dakins, J. E. Toll, M. J. Small, and K. P. Brand, "Risk-based environmental remediation: Bayesian Monte Carlo analysis and the expected value of sample information," Risk Analysis **16** (1), 67-79 (1996).

24. K. M. Thompson and J. S. Evans, "The value of improved national exposure information for perchloroethylene (Perc): A case study for dry cleaners," Risk Analysis **17** (2), 253-271 (1997).

25. C. Y. Lin, A. Gelman, P. N. Price, and D. H. Krantz, "Analysis of local decisions using hierarchical modeling, applied to home radon measurement and remediation," Statistical Science **14** (3), 305-328 (1999).

26. S. M. Bartell, R. A. Ponce, T. K. Takaro, R. O. Zerbe, G. S. Omenn, and E. M. Faustman, "Risk estimation and value-of-information analysis for three proposed genetic screening programs for chronic beryllium disease prevention," Risk Analysis **20** (1), 87-99 (2000).

27. K. M. Thompson and J. D. Graham, "Going beyond the single number: Using probabilistic risk assessment to improve risk management," Human and Ecological Risk Assessment **2** (4), 1008-1034 (1996).

28. D. Samson, A. Wirth, and J. Rickard, "The Value of Information from Multiple Sources of Uncertainty in Decision-Analysis," European Journal of Operational Research **39** (3), 254-260 (1989).

29. K. P. Brand and M. J. Small, "Updating uncertainty in an integrated risk assessment: Conceptual framework and methods," Risk Analysis **15** (6), 719-731 (1995).

30. National Research Council, *Science and Judgment in Risk Assessment* (National Academy Press, Washington, D.C., 1994).

31. K. M. Thompson, "Variability and uncertainty meet risk management and risk communication," Risk Analysis **22** (3), 647-654 (2002).

32. K. M. Thompson, "Developing univariate distributions from data for risk analysis," Human and Ecological Risk Assessment **5** (4), 755-783 (1999).

33. D. Vose, *Risk Analysis: A Quantitative Guide* (John Wiley & Sons, Chichester, England, 2000).

34. A. C. Cullen and H. C. Frey, *Probabilistic Techniques in Exposure Assessment: A Handbook for Dealing with Variability and Uncertainty in Models and Inputs* (Plenum Press, New York, 1998).

35. J. C. Felli and G. B. Hazen, "Sensitivity analysis and the expected value of perfect information," Medical Decision Making **18** (1), 95-109 (1998).

36. K. Claxton, P. J. Neumann, S. Araki, and M. C. Weinstein, "Bayesian value-of-information analysis - An application to a policy model of Alzheimer's disease," International Journal of Technology Assessment in Health Care **17** (1), 38-55 (2001).

37. A. C. Miller and T. R. Rice, "Discrete Approximations of Probability Distributions," Management Science **29** (3), 352-362 (1983).

38. B. P. Carlin, "Analysis of local decisions using hierarchical modeling, applied to home radon measurement and remediation - Comment," Statistical Science **14** (3), 328-337 (1999).

39. National Research Council, *Valuing Health Risks, Costs, and Benefits for Environmental Decision Making* (National Academy Press, Washington, DC, 1990).

40. K. Viscusi, *Fatal Tradeoffs: Public and Private Responsibilities for Risk* (Oxford University Press, New York, NY, 1992).

41. J. K. Hammitt, "Valuing mortality risk: Theory and practice," Environmental Science & Technology **34** (8), 1396-1400 (2000).

42. J. K. Hammitt, "Can More Information Increase Uncertainty?," Chance **8** (3), 15-17, 36 (1995).

43. J. K. Hammitt and A. I. Shlyakhter, "The expected value of information and the probability of surprise," Risk Analysis **19** (1), 135-152 (1999).

44. R. T. Clemen and R. L. Winkler, "Limits for the Precision and Value of Information from Dependent Sources," Operations Research **33** (2), 427-442 (1985).

45. K. M. Thompson, M. Segui-Gomez, and J. D. Graham, "Validating analytical judgments: the case of the airbag's lifesaving effectiveness," Reliability Engineering & System Safety **66** (1), 57-68 (1999).

46. M. G. Morgan and M. Henrion, *Uncertainty: A Guide to Dealing with Uncertainty in Quantitative Risk and Policy Analysis* (Cambridge University Press, New York, NY, 1990).

47. National Research Council, *Understanding Risk: Informing Decisions in a Democratic Society* (National Academy Press, Washington, DC, 1996).

48. M. Gold, J. Siegel, L. Russel, and M. Weinstein, *Cost-effectiveness in Health and Medicine* (Oxford University Press, New York, NY, 1996).

49. R. A. Howard, "An Assessment of Decision Analysis," Operations Research **28** (1), 4-27 (1980).

Figure 2.1: Schematic of the optimal bid problem

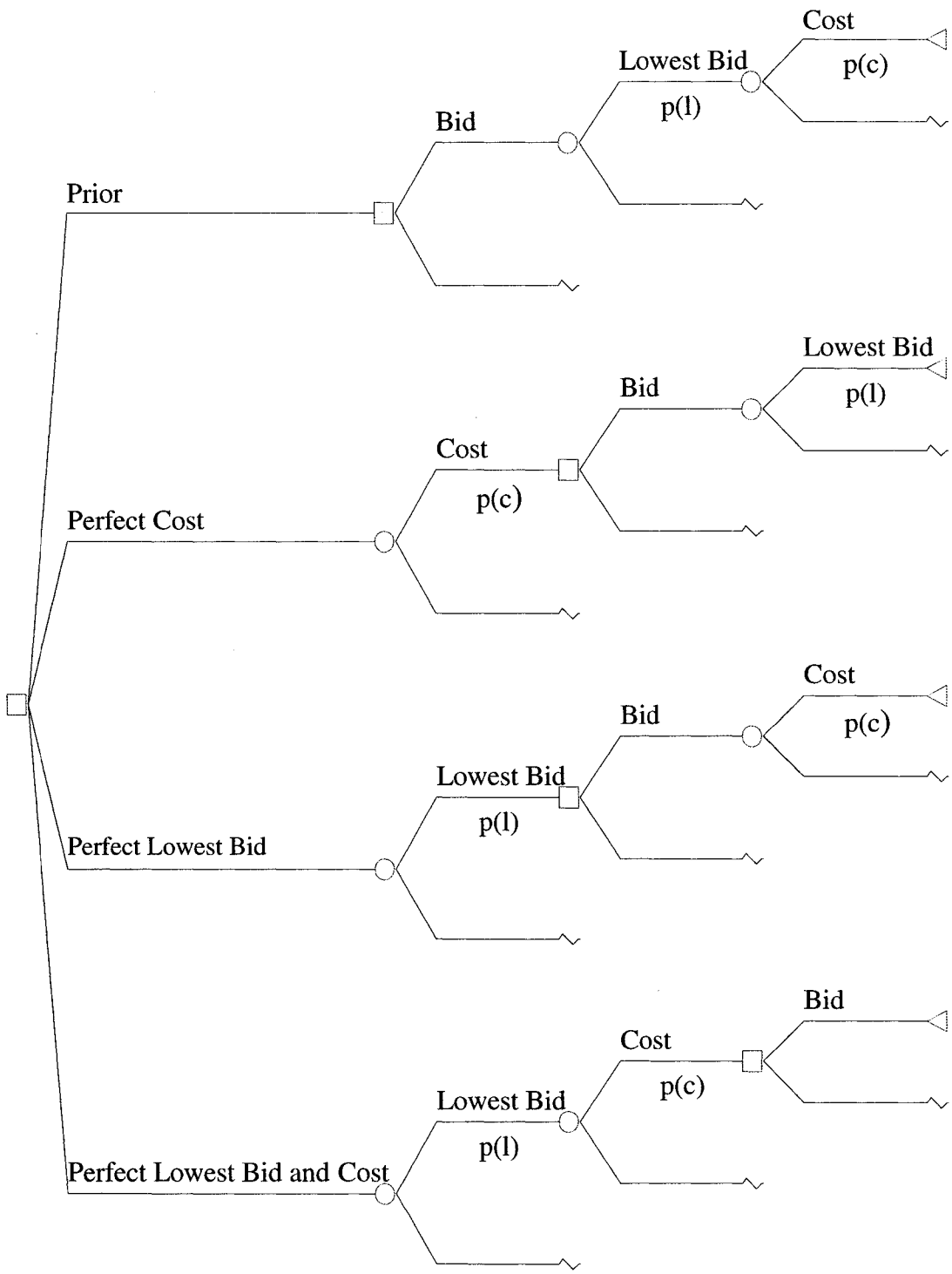

Table 2.1: Solutions to the optimal bid problem in Howard (1966)

	Scenarios (000s)	Expected Profit				EVPI		
		Prior	Cost	Lowest	Both	Cost	Lowest	Both
Analytical	-	0.281	0.292	0.563	0.583	0.010	0.281	0.302
Discretize								
n = 10	20	0.316	0.325	0.553	0.575	0.009	0.237	0.259
n = 32	204.8	0.293	0.302	0.559	0.579	0.009	0.266	0.287
n = 100	2,000	0.281	0.292	0.555	0.576	0.010	0.274	0.295
Simulate (1 set)								
n = 100	20	0.264	0.295	0.558	0.569	0.031	0.294	0.304
n = 1,000	200	0.280	0.293	0.559	0.575	0.013	0.279	0.295
n = 10,000	2,000	0.282	0.292	0.559	0.580	0.010	0.277	0.299
Simulate (10 sets)								
n = 100	200							
Mean		0.286	0.295	0.559	0.574	0.009	0.272	0.288
95% C.I.		0.274-0.298	0.295-0.295	0.558-0.559	0.567-0.581	-0.003-0.021	0.260-0.285	0.278-0.297
Range		0.264-0.319	0.295-0.296	0.558-0.560	0.558-0.589	-0.024-0.031	0.240-0.294	0.262-0.304
n = 1,000	2,000							
Mean		0.283	0.293	0.559	0.580	0.010	0.276	0.297
95% C.I.		0.281-0.285	0.293-0.293	0.559-0.559	0.578-0.583	0.007-0.012	0.273-0.278	0.298-0.298
Range		0.280-0.289	0.292-0.293	0.558-0.559	0.575-0.585	0.003-0.013	0.269-0.279	0.294-0.299

Table 2.2: Attributes of EHRM VOI analyses (grouped by solution method)

	Discrete					Discretized						Simulation				
	Lave[11]	Lave[12]	Lave[13]	Omenn[14]	Omenn[15]	North[16]	Finkel[17]	Evans[18]	Reichard[19]	Taylor[20]	Chao[21]	Dakins[22]	Dakins[23]	Thompson[24]	Lin[25]	Bartell[26]
Types of VOI analyses																
EVPI						x	x		x	x		x	x	x		
EVPXI							x		x					x		
EVSI	x	x	x	x	x					x	x		x		x	
EVSXI								x	x							x
Decision model																
No of actions	2	2	2	2	2	4	3	5	2	2	∞	∞	∞	11	2	2
No of info collection strategies	2	2	2	3	2	0	0	2	4	3	2	0	4	0	4	4
Valuation of outcomes																
Lump sum	x	x	x		x						x					
Premature death averted				x		x	x	x	x	x				x		x
Morbidity prevented						x										x
Ecological damage						x										
Model inputs																
No of uncertain inputs	1	1	1	1	1	2	2	2	2	1	3	6	1	14	1	7
Includes subgroups						x		x						x	x	
Probability distributions																
Discrete set	x	x	x	x	x						x					x
Beta																x
Binomial										x						
Lognormal						x	x	x	x	x	x			x	x	
Normal												x	x			
Triangular												x		x		x
Uniform											x	x		x		x
Empirical														x		
Other						x			x				x			
Source of data																
Expert judgment								x								
Model output									x				x		x	

Table 2.3: Valuation of outcomes in EHRM VOI analyses (grouped by solution method)

	Baseline	Low	High	Outcome	Year Dollar	Discount Rate
Discrete						
Lave and Omenn[11]	$10 million	-	-	Lump sum per unregulated carcinogen	NR	NR
Lave and Omenn[12]	$10 million	-	-	Lump sum per unregulated carcinogen	NR	NR
Lave et al.[13]	$10 million	-	-	Lump sum per unregulated carcinogen	NR	NR
Olson[14]	$2 million	-	-	Cancer death (generic)	1986	0%
Omenn et al.[15]	$10 million	-	-	Lump sum per unregulated carcinogen	NR	NR
Discretized Continuous						
North and Merkhofer[16]	$30,000	-	-	Premature death of chronically ill from air pollution	NR	NR
Finkel and Evans[17]	$1 million	$250,000	$4 million	Cancer death (generic)	NR	NR
Evans et al.[18]	$3 million	$1 million	$10 million	Cancer death from radon	NR	3%
Reichard and Evans[19]	$1 million	$50,000	$10 million	Cancer death from arsenic	NR	5%
Taylor et al.[20]	$10 million	-	-	Cancer death (generic)	NR	5%
Chao et al.[21]	$1 billion			Lump sum per ppm of ozone if peak concentration exceeds 0.12 ppm	1989	5%
Simulation						
Dakins et al.[22]	-	-	-	No health	1985	0%
Dakins et al.[23]	-	-	-	No health	1985	0%
Thompson and Evans[24]	$3 million	$1 million	$10 million	Cancer death from perc	1989	5%
Lin et al.[25]*	$210,000	-	-	Cancer death from radon	NR	5%
Bartell et al.[26]	-	$12,200	$16 million	Illness and death from CBD	NR	0%-7%

NR = Note reported, * Implied by the standard chosen

Appendix

A1. S-Plus Code for Optimal Bid VOI Problem

A1.1 Discretization

```
# Adjust these values
  increment <- 0.01 # increment of bids
  n <- 100          # level of discretization of cost and lowest bid
  init <- -666      # initial value

# Assign bid values
  m <- 2/increment  # number of bids
  bid <- seq(0, by=increment, length=m)

# Discretize cost and lowest bid values
  cost <- matrix(seq(1/n/2, by=1/n, length=n), ncol=1)
  lowest <- matrix(seq(1/n, by=2/n, length=n), nrow=1)

# Initialize max EV{profit} for each cost value(nx1 matrix)
  E.prior <- matrix(rep(init, m), ncol=1)
# Initialize max EV{profit} for each lowest bid value(nx1 matrix)
  E.cost <- matrix(rep(init, n),  ncol=1)
# Initialize EV{profit} for each bid (mx1 matrix)
  E.lowest <- matrix(rep(init, n), nrow=1)
# Initialize max EV{profit} for each cost-lowest bid combination (nxn matrix)
  E.both <- matrix(rep(init, n*n), nrow=n)

# Define Function "Max Value"; compare two values and return the larger value
   Max.Value <- function (new, old){
    ifelse(new > old, new, old)
  }

# Repeat for each bid value
  for (i in 1:m){
  # Calculate profit for cost-lowest bid combination given a bid
    profit <- (bid[i]-cost)%*%ifelse(lowest - bid[i] > 0.00001, 1, 0)

  # Calculate expected profit for this bid
    E.prior[i] <- mean(profit)

  # Replace value if the mean profit given cost is greater
    E.cost <- Max.Value(profit%*%rep(1,n)/n, E.cost)

  # Replace value if the mean profit given lowest bid is greater
    E.lowest <- Max.Value(rep(1,n)%*%profit/n, E.lowest)

  # Replace value if the profit from this bid is greater
    E.both <- Max.Value(profit, E.both)
  }

# Report Values
  max(E.prior)
  mean(E.cost)
  mean(E.lowest)
  mean(E.both)
```

A1.2 Simulation

```
# Adjust these values
  increment <- 0.01 # increment of bids
  n <- 1000         # number of samples per set
  set <- 10         # number of sets
  init <- -666      # initial value

# Assign bid values
  m <- 2/increment  # number of bids
  bid <- matrix(seq(0, by=increment, length=m), nrow=1)

# Upload input values from simulation in @Risk
  cost <- scan("D:\\Data\\cost.txt")
  lowest <- scan("D:\\Data\\lowest.txt")

# Distribute samples into matrix of n-rows
  cost <- matrix(cost, nrow=n, byrow=T)
  lowest <- matrix(lowest, nrow=n, byrow=T)

# Initialize EV{profit} from prior info for each set
  EV.prior <- rep(init, set)
# Initialize EV{profit} from cost info for each set
  EV.cost <-rep(init, set)
# Initialize EV{profit} from lowest bid info for each set
  EV.lowest <-rep(init, set)
# Initialize EV{profit} from both info for each set
  EV.both <-rep(init, set)

# column of m ones
  m.ones <- rep(1,m)
# column of n ones
  n.ones <- rep(1,n)

# Repeat for each set
  for (i in 1:set){
  # Initialize indicator of whether bid wins (nxm matrix)
    win <- matrix(rep(init, n*m), nrow=n)
  # Initialize profit for each bid and iteration (nxm matrix)
    profit <- matrix(rep(init, n*m), nrow=n)
  # Initialize profit given perfect cost information (nxm matrix)
    profit.c <- matrix(rep(init, n*m), nrow=n)
  # Initialize profit given perfect lowest bid information (nxm matrix)
    profit.l <- matrix(rep(init, n*m), nrow=n)
  # Initialize profit given prior information for each bid (m values)
    p.prior <- rep(init,m)
  # Initialize profit given cost information for each iteration (n values)
    p.cost <- rep(init,n)
  # Initialize profit given lowest bid for each iteration (n values)
    p.lowest <- rep(init,n)
  # Initialize profit given both for each iteration (n values)
    p.both <- rep(init,n)

  # Indicate whether bid wins for each bid and iteration
    win <- ifelse(n.ones%*%bid < lowest[,i]%*%t(m.ones),1,0)

  # Expected value of indicator for each bid (i.e., probability of win)
    m.win <- t(n.ones)%*%win/n

  # Profit for each bid and iteration
    profit <- (n.ones%*%bid - cost[,i]%*%t(m.ones))*win
```

```
  # Profit for each bid and iteration given probability of winning
    profit.c <- (n.ones%*%bid - cost[,i]%*%t(m.ones))*(n.ones%*%m.win)

  # Profit for each bid and iteration given expected value of cost
    profit.l <- (n.ones%*%bid - mean(cost[,i]))*win

  # Profit for each bid
    p.prior <- t(n.ones)%*%profit/n

  # Maximum EV{profit} for each iteration
    for (j in 1:n){
    p.cost[j] <- max(profit.c[j,])
    p.lowest[j] <- max(profit.l[j,])
    p.both[j] <- max(profit[j,])
    }

  # EV{profit} with prior information
    EV.prior[i] <- max(p.prior)

  # EV{profit} with perfect cost information
    EV.cost[i]<-mean(p.cost)

  # EV{profit} with perfect lowest bid information
    EV.lowest[i]<-mean(p.lowest)

  # EV{profit} with perfect information about both
    EV.both[i]<-mean(p.both)
  }

# Calculate EVPI
  EVPI.cost <- EV.cost-EV.prior
  EVPI.lowest <- EV.lowest-EV.prior
  EVPI.both <- EV.both-EV.prior

# Store values for all sets in one data set
  EV<-cbind(EV.prior, EV.cost, EV.lowest, EV.both, EVPI.cost, EVPI.lowest,
EVPI.both)

# Define Function "Summary.Stats"; calculate summary stats including 95% CI
  Summary.Stats <- function(data){
  menuDescribe(data, print.p=F, conf.lim.mean.p = T, conf.level.mean = 0.95)
  }

# Calculate and store summary statistics
  Stat.EV <- Summary.Stats(EV)
```

A2. Annotated Bibliography of VOI Applications in EHRM

Bartell et al. (2000) [26] evaluate the value of a screening program to prevent chronic beryllium disease (CBD) from occupational exposure. The analysis evaluates the value from resolving the uncertainty in the presence or absence of a genetic polymorphism that makes an individual susceptibility to CBD using a probabilistic risk assessment. They use a point estimate for the prior prevalence of susceptible individuals and seven uncertain inputs characterized by various parametric distributions such as sensitivity and specificity of the genetic screening test, and evaluate expected values using a simulation approach. They compare three different strategies for screening to doing nothing, where a "positive" screening result leads to an intervention that will lead to either early treatment of the disease or prevention of exposure to beryllium. A case of CBD prevented is valued at four different values, ranging from a low estimate of $12,200 which considers only future medical costs averted discounted at 7%, to a high number of $16,300,000 which is a high estimate of the value of a statistical life with no discounting (no year dollar given). The lower the value of CBD avoided, the higher the occupational prevalence of CBD susceptibility must be to justify any screening program. Their analysis shows for value of CBD avoidance greater than $1,450,000, the EVSI net of screening cost for all three options for screening is positive at current estimates of occupational prevalence.

Chao et al. (1994) [21] compare an one stage strategy to a two stage strategy that incorporates information learned in the first stage to calculate the "value of flexibility" in a hypothetical management decision to control tropospheric ozone. The decision is choosing the optimal levels of control of both nitrogen oxides and volatile organic compounds to minimize total societal cost where ozone is estimated to have an impact of $10 billion per year per ppm if peak ozone concentration exceeds .12 ppm; health risk is not modeled explicitly. The uncertainty in current emission rates are expressed as uniform distributions, and uncertainty in the photochemical model expressed as a lognormal distribution. The analysis models information available after the first stage as

a sampling outcome with assumed accuracy, but does not consider the cost of collecting such information. The authors used a decision tree to solve the problem, for each stage discretizing the emission reduction decisions into five choices each, the emission reduction to three branches each, and model error into five branches thereby evaluating a total of 1,265,625 scenarios. Reduction in cost from incorporating the information gained in the first stage in the two stage policy, or the EVSI, is $9 million (no year dollar given).

Dakins et al. (1994) [22] evaluate the remediation of PCB contaminated sediments in New Bedford Harbor, Massachusetts. Unlike the previous studies that explicitly value health consequences, the objective of this policy decision is to choose an optimal level of dredging which will minimizes remediation cost while meeting a health based standard for PCB concentration in fish. The analysis assumes that the correct level of remediation will be known in the future, and if under remediation has occurred, additional remediation to meet the standard must be completed and would incur additional penalties such as the fishery remaining closed for longer and additional cost of remobilizing research and remediation efforts. The analysis includes six uncertain inputs such as PCB concentration in the sediment, average water temperature, and growth rate of flounder each described by a parametric distribution such as the normal, triangle, and uniform. It assumed independence of the uncertain inputs, and used Monte Carlo simulation using Latin hypercube sampling to predict the total PCB body burden in flounders. They estimate that EVPI, from resolving all uncertainties in the model, is $16 million in 1985 dollars.

Dakins et al. (1996) [23] expand on the previous analysis by calculating the EVSI from sampling founder to measure total PCB body burden. They model the prior distribution for body burden by simulating 50 replications using the model established in Dakins et al. (1994)[22]. They conduct a preposterior analysis to evaluate the EVSI from sampling two, five, and ten randomly selected flounder from New Bedford Harbor. They assume that the likelihood of observing a particular set of body burden measurements is normally distributed given a true value of total body burden. They estimate that the gross EVSI

(i.e., not considering information collection costs) is $9.4 million for the two sample scheme, $1.4 million for the five sample scheme and $11.5 million for the ten sample scheme in 1985 dollars. They also test the robustness of sampling just 50 values to establish the prior distribution by repeating the calculation five times using different random seeds and find that the expected losses vary within a range of $800,000, which they note is small relative to the overall expected loss.

Evans et al. (1988) [18] use the framework laid out in Finkel and Evans (1987)[17] to model individual homeowner's decision to monitor for radon in their homes to assist in choosing one of five remediation actions. They formally elicit expert judgment to characterize the uncertainty surrounding exposure and potency of radon in causing cancer. They also account variability in radon exposure by setting different distributions based on region of the country and characteristic of the home, and additional variability in potential benefits from monitoring by analyzing the VOI to household of four representative demographic compositions. Since monitoring reduces but not eliminate uncertainty about exposure, they analyze the EVSXI for exposure for three different levels of prior information about radon concentration available to the household: no data available, regional data available, and data from a neighbor with a similar home. Valuing a life at $3 million and using a real discount rate of 3% they find that even at a seemingly insignificant monitoring cost of $50, there are many households that would not benefit from monitoring since the gross EVSXI in present value is less than $50.

Finkel and Evans (1987)[17] note the lack of application of VOI methods to environmental problems, and describe the VOI framework for environmental management and illustrate the methods with a hypothetical risk management problem. Their approach is rooted in risk analysis methods and models uncertainty about the health risk from a contaminant, which is the product of two components: dose and exposure. Both components are modeled as lognormal distributions, therefore the uncertainty about risk is also lognormal. They analyze three alternatives for controlling a hypothetical contaminant, and value each premature death at $1 million. They evaluate how EVPI and EVPXI for

dose vary with different assumptions about the magnitude of the uncertainty and the estimate used for the value of life

Lave and Omenn (1986) [11] present a framework for evaluating the value of short-term tests for carcinogenicity of chemicals to inform regulatory decision making. The approach identifies optimal battery of short term tests based on the accuracies of a test battery, and the trade-off between false negative and false positive misclassification of chemicals. The only uncertain input in the simple calculation is whether the chemical is carcinogenic or not; the study makes back-of-the-envelope calculations using point estimates for accuracy of tests based on empirical evidence, and rough guesstimates of costs of misclassification and prevalence of carcinogenic chemicals. The paper further discusses optimal "cut point" for considering a test result "positive" and cost-effectiveness of different battery of tests. The study finds that even with potential costs from misclassification, using short term tests as a basis for regulating chemicals as carcinogens may be superior to tolerating unregulated carcinogens absent animal bioassay results from a societal perspective.

Lave and Omenn (1988) [12] further explore the societal value of short term tests using a threshold analysis to show how sensitive/specific the tests must be to have a positive information value, using several different point estimates for prevalence of carcinogens, and relative screening cost. The paper finds that most accurate test may not be the most desirable testing strategy from a societal perspective, nor the least expensive test.

Lave et al. (1988) [13] consider the information value of the rodent bioassay by performing a threshold analysis for input values that yield positive information value. The decision model is a choice between three actions: classify a chemical as non-carcinogen without a bioassay, test the chemical, and classify a chemical as carcinogen without a bioassay. Like the previous applications, the only uncertainty input in the calculation is whether the chemical is carcinogenic or not, and makes back-of-the-envelope calculations using point estimates for accuracy of tests based on empirical evidence, and rough guesstimates of the cost of misclassification and prevalence of

carcinogenic chemicals. The objective is to minimize social cost, and they use three-way sensitivity analyses on various parameters to identify general conditions under which a rodent bioassay should be used for carcinogenic testing. The threshold analyses show that under many plausible values of inputs, conducting the bioassay would be prudent. On the other hand, if the prior belief of carcinogenicity is sufficiently high or concordance of animal and human test results sufficiently low, the strategy to classify the chemical as a carcinogen without further testing dominates the decision. In these cases, even if the bioassay shows a negative result, the optimal strategy is to classify the chemical as a carcinogen.

Lin et al. (1999) [25], like Evans et al. (1988) [18], evaluate the VOI from measuring radon in private homes to assist in the decision to take remediation action or not. However, rather than explicitly valuing willingness to pay (WTP) to reduce risk, the objective is to minimize total cost (including residual risk after remediation) based on an action level, the level of exposure above which one should remediate, that is determined by household composition, a household's risk preference and WTP for risk reduction. In addition, the authors account for variability in risk of cancer based on gender and smoking status. For the example base case analysis, the authors chose an action level established by the U.S. EPA of 4 pCi/L, which implies a value of $210,000 per life (no year dollar given), assuming a household consisting of the average number of male and female smokers and never smokers in the United States. The sole uncertain input in their model is the concentration of radon, and is characterized by a lognormal prior distribution based on a hierarchical linear regression model that fits county level explanatory variables to radon measurements, yielding parameter values that vary by county and housing type. For the base case, the authors assume that long term monitoring produces an unbiased, lognormally distributed estimate of concentration such that the posterior distribution of true concentration given measurement is also lognormally distributed. They use a simulation technique to calculate the expected losses from monitoring, remediating without monitoring and doing nothing for different levels of prior estimates of concentration. Even at the low cost of $50 for monitoring, only 27% of households

should monitor, while 68% of households should do nothing, and 5% should remediate immediately.

North and Merkhofer (1976)[16] compared four alternative strategies for controlling pollution emissions from electric power plants with the objective of minimizing total social costs. They evaluate the value of simultaneously resolving two uncertainties in the model: how a unit of emission translates to ambient concentration and the total health cost per unit increase in suspended sulfate concentration, which are assumed to be independent in the analysis. The characterizations are based on the authors' subjective judgment on extreme values, and are modeled to represent the 5th and 95th percentile points on the cumulative probability distribution. They provide a sketch of the cumulative distribution for the ambient sulfate concentration increment and assume a lognormal distribution for the total health cost. The optimization problem is solved for three types of representative power plants: existing coal plant in "rural" area, new construction in "rural" area, and oil burning plant (originally designed for coal) in urban east coast location. The estimate a rough estimate of $250 million per year (no year dollar given) to as the expected value of eliminating uncertainties about both the relationship between emissions and ambient concentration and the health consequences of sulfur emissions (i.e., EVPI).

Olson (1990) [14] derives the "optimal screening rule" for carcinogenicity testing, where the objective is to maximize expected net social benefits. It focuses on how much toxicological information should be collected before taking regulatory action rather than which chemicals should be regulated first. Again, the only uncertain input is whether the chemical is carcinogenic or not, and the study uses a point estimate for prior probability of carcinogenicity, and unlike the previous papers, explicitly calculate the value of a cancer prevented – $2 million per life in 1986 dollars. The study proposes a two tiered system, first conducting a mutagenicity test then conducting a bioassay, if the expected value of testing exceeds the expected value of taking immediate action. Point estimates for the sensitivity and specificity of mutagenicity and bioassay tests are derived from empirical data, and the framework is illustrated using a hypothetical example.

Omenn et al. (1995) [15] use the framework from Lave et al. (1988) [13] to calculate the social cost of 13 different approaches for predicting results of a life-time rodent bioassay developed through the Carcinogenic Prediction Challenge sponsored by the NTP. They use a hypothetical point estimate of prior probability and the sensitivity and specificity values implied by the strategies for 44 chemicals, and a rough estimates of consequences to determine social costs for each approach. They also calculate the social costs from different "cut points" for a positive results from one prediction method. The analysis shows that "accuracy" is not the socially optimal criterion for determining how "good" a prediction is if the consequences of misclassification (false negative and false positives) are not equal.

Reichard and Evans (1989) [19] consider the value of monitoring in remediation decision for groundwater that may be contaminated by arsenic. It takes a societal perspective in their analysis, and uses a risk assessment approach following the framework of Finkel and Evans (1987)[17] and uses a baseline value of life set at $1,000,000 (no year dollar given). There are two uncertain inputs in the VOI analysis: the potency of arsenic in causing cancer, represented by a lognormal distribution based on epidemiological data, and the exposure to arsenic in the water, characterized by a lognormal distribution fitted to the output of a hydrogeologic model. They calculate both the EVPI and EVPXI for exposure information, as well as EVSXI for exposure from three different monitoring strategies compared to no monitoring. The analysis shows the EVSXI from the most aggressive is smaller than the cost of monitoring, however, the other two strategies yield positive VOI.

Taylor et al. (1993) [20], unlike the previous studies, assess the animal bioassay's ability to determine magnitude of cancer causing potential, and explicitly incorporate exposure to a chemical and effectiveness of control strategies in assessing social costs. They consider four information collection strategies: (1) do nothing, (2) use test results from a subchronic bioassay as a proxy for cancer potency, (3) use test results from a long-term bioassay to calculate cancer potency, and (4) apply control strategy without any testing.

The objective is the minimization of a social cost function and the one uncertain input in the model is carcinogenic potency of a chemical. The prior distribution of potency is based on the results of the first 213 NTP mouse bioassays. Since only half of the chemicals were determined to have positive results, for the base case analysis, the distribution is characterized as the sum of a delta function at zero potency with a probability mass of 50%, and a lognormal distribution fit to the statistically significant test results and normalized so that the entire distribution integrates to unity. They model likelihood of test results as a Binomial distribution and create a matrix of values to solve for the values of the posterior distribution. Hypothetical examples are given based on plausible values from empirical evidence to illustrate the framework. The analysis uses a threshold approach to show conditions under which value of information would be positive. Since the analysis explicitly includes exposure in the model, its importance in determining VOI can be measured. For a range of exposure values, both the subchronic and chronic animal tests have a positive information value. For small exposures, however, information from testing is unlikely to change the decision maker's optimal strategy – not control the exposure – and therefore yields little information value.

Thompson and Evans (1997) [24] evaluate the value of national exposure information about perchloroethylene (perc) used in dry cleaning. Unlike other applications, the analysis compared regulating perc exposure at three different levels of decision making: individual dry cleaning facilities, by particular dry cleaning machine category (defined by type and size), and by particular machine type. Similar to the framework established in Finkel and Evans (1987)[17], the objective is to choose the pollution control option that minimize overall social cost including control costs and explicitly modeling and valuing risk of cancer from perc exposure. They considered variability by modeling risks to four distinct populations: dry cleaning workers, families of workers, consumers of dry cleaning services, and the general public from ambient exposure and valued each premature death from caner at $3 million. The analysis considered fourteen uncertain inputs characterized by various parametric distributions and an empirical distribution, and calculated the EVPI and EVPXI for various uncertain inputs using simulation. The EVPI ranges from $4 million per year to $8 million per year in 1989 dollars, depending on what

level the regulatory decision is made. It notes that the EVPI estimates are an upper bound on the EVSI from collecting exposure information, however, it may also be an underestimate if the information would be useful in other decision contexts not considered in the analysis.

Section 2: Value of Toxicological Information in Improving Health

Chapter 3: Optimal Stopping Strategy for Tiered Chemical Testing – A Value of Information Approach

1. Introduction

A 1997 report by the Environmental Defense called "Toxic Ignorance," brought national attention to the lack of toxicity information on many of the high production volume (HPV) chemicals used or produced in the United States.[1] In response, the U.S. Environmental Protection Agency (EPA) conducted a comprehensive study to review the public availability of toxicity tests.[2] The study searched for six types of tests that the Organization for Economic Cooperation and Development (OECD) considers to be minimum information needed to screen potentially hazardous chemicals for further toxicological testing[3] and found that of the nearly 3,000 HPV chemicals, 43 percent of the chemicals had no basic toxicity information while only 7 percent had a complete set of basic information. The results were more encouraging for the approximately 500 chemicals used in consumer products; only 7 percent had no basic information while nearly 25 percent had all six sets of information. Nonetheless, the study highlighted the dearth of information on chemicals the public may be highly exposed to. In response, the EPA initiated the Chemical Right-to-Know Initiative (ChemRTK) in April of 1998 to gather basic toxicity information for all of the HPV chemicals in the United States.[4]

Executive Order 13045 underscored the potential for children to suffer disproportionately from health and safety risks due to differences in their physiology and patterns of exposure, and directed each federal agency to make assessments of whether elevated risks exist.[5] Since the basic test information gathered through the HPV program may not be enough to adequately assess health risks to children, as part of the ChemRTK initiative, the EPA initiated the development of a children's health chemical

testing program and solicited public input on how best to collect additional toxicological information beyond the HPV requirements. Following the input from stakeholders and the Science Advisory Board, the EPA formally announced the Voluntary Children's Chemical Evaluation Program (VCCEP) and asked manufacturers to sponsor the collection of information for twenty-three chemicals identified for the pilot phase of the program.[6]

The VCCEP consists of a battery of tests divided into three tiers as indicated in Table 3.1. The first tier includes screening tests to assess qualitative information on the potential toxic and carcinogenic effects and corresponds to the tests required for the HPV screening program. It will yield a determination of mutagenicity and acute toxicity measures such as lethal dose 50 (LD50), the dose level of a chemical that causes the death of 50% of the test animals when given all at once. The second tier includes tests for additional qualitative hazard data as well as data to establish dose-response relationships for non-cancer risks, and the determination of the maximum tolerated dose (MTD), the highest dose level that can be tolerated by the test animal over its lifetime, which will be used to set testing doses for long-term bioassay in the third tier. The third tier includes long-term animal bioassays to refine non-cancer dose-response relationships as well as carcinogenicity. Developmental toxicity and reproductive effects in the second tier and developmental neurotoxicity in the third tier are the only tests that are specifically designed to address prenatal and neonatal health.

In conjunction with the toxicity information, the VCCEP program collects exposure information for each chemical in tiers. The first tier is a screening level assessment designed to derive a "conservative" estimate of exposure to children or

perspective parents. The second and third tier assessments should estimate central tendency of exposure as well as estimates of "high" exposure. For each tier a risk assessment will integrate the available toxicity results and exposure information, and the sponsors will develop a data needs assessment to identify additional information that would be necessary to "adequately assess the potential risks to children."[6] EPA will then make a determination about whether the risks have been adequately assessed. However, the VCCEP program currently does not have clearly defined criteria to determine when information is "adequate."

Nearly two decades ago, the National Research Council published a report on priority setting for toxicity testing recognizing the importance of a systematic approach to reduce the uncertainty about a chemical's hazard that takes into consideration time and budget constraints. Moreover, it recognized the importance of a value of information (VOI) approach, noting: "the contribution of this concept is in making explicit that the goal of the testing program should be embodied in the priority-setting system."[7] Indeed, decision analysts have argued that "placing a value on the reduction of uncertainty is the first step in experimental design, for only when we know what it is worth to reduce uncertainty do we have a basis for allocating our resources in experimentation designed to reduce the uncertainty."[8] The VOI approach considers both the value of collecting information in terms of making better management decisions that lead to increase in net benefits and the cost of collecting information. Since a stated goal of the VCCEP program is to "ensure that health effects and exposure data are made available to allow EPA and others to evaluate the risks of these chemicals so that mitigation measures may be taken as appropriate,"[6] it would be constructive to explore how the application of a

VOI framework can provide some guidance to decision makers in determining when to require additional testing in a tiered program such as the VCCEP.

VOI analysis requires modeling a probability distribution for the prior belief about the uncertain input and the belief about the accuracy of the information collected. For carcinogenicity, there are empirical relationships established by analyses of chronic animal bioassay test results from the National Cancer Institute/National Toxicology Program (NCI/NTP) and other tests from the general literature that can be used to predict the result of long-term bioassays. A Tier 1 test such as mutagenicity is highly predictive of whether a chemical is found to be carcinogenic.[9] In addition, LD50 has been found to be highly correlated to carcinogenic potency.[10-12] Likewise, MTD from tier 2 testing has been found to be highly correlated to potency.[10,13] Unfortunately, the correlations between test results of the various non-cancer tests are not well established, though there has been some empirical work on the relationship between LD50 and reference dose.[14] Therefore the paper will specifically explore how the carcinogenicity data collected through the VCCEP may be used to inform risk management decisions. This analysis will explore the optimal stopping criteria for a chemical where tier 1 screening data have been collected.

Section 2 reports the methods including the decision analytic framework for determining optimal actions, the cancer risk model, the Bayesian updating of potency estimates, the calculation of the value of information, and a description of the inputs for four hypotherical cases that represents two extreme cases of test results from the first tier – non-mutagen with low acute toxicity and a mutagen with highly acute toxicity – and two intermediate cases that will be used to illustrate the VOI framework. Section 3

reports the results of the analysis including the distribution of the potency estimates following test results, the expected value of information, the optimal testing decision given tier 1 information, and sensitivity of the results to various assumptions in the base case analysis. Section 4 offers some interpretation and discussion of the result including policy insights, limitations of the analysis, and areas for further research.

2. Methods

2.1 Decision Analytic Framework

VOI analysis requires modeling the available set of actions, characterizing prior belief about uncertain inputs and belief about the accuracy of the information collected (i.e., the likelihood of observing a particular test result), and quantifying all relevant consequences of actions from the perspective of the decision maker using a common metric. Several previous analyses used a simple decision analytic framework with point estimates to determine whether or not toxicological testing would correctly distinguish whether a chemical was a carcinogen or not. [15-17] Taylor et al.[18] added more complexity to the evaluation by assessing the animal bioassay's ability to determine magnitude of cancer causing potential, and explicitly incorporate exposure to a chemical and effectiveness of control strategies in assessing social costs. They developed hypothetical examples based on plausible values from empirical evidence to illustrate the framework. The analysis in this paper expands on the previous analyses and explores the optimal testing strategy in the context of an actual tiered testing program.

This analysis uses the perspective of an expected net benefits maximizing decision maker (NBMDM), the "traditional" decision maker used in decision analyses.

The NBMDM regulates a chemical based on a subjective prior assessment of potency updated by indirect measures in addition to "hard" data from animal bioassay, uses the maximum likelihood estimate of potency to determine possible population risk, and chooses the level of regulation that will maximize net societal benefits. Figure 3.1 represents a simplified schematic of the testing decision for a NBMDM; a square represents a decision node, a circle represents a chance node, and a triangle is a terminal node. The NBMDM uses the empirical relationship between test results in each tier to refine the estimate of potency.[1] The figure represents five testing strategies given the results of the tier 1 testing of the VCCEP (i.e., acute toxicity and mutagenicity results of HPV program): (1) hypothetical collection of perfect information, which will serve as an upper bound for the willingness to pay for reducing uncertainty to make a better regulatory decision; (2) a tiered approach of the VCCEP where MTD data are collected in the second tier, and the NBMDM will decide whether to make a regulatory decision based on the MTD result or continue to test the chemical in a long-term rodent bioassay; (3) conducting the bioassay regardless of the MTD result; (4) stopping after the subchronic testing regardless of the MTD result; and (5) conduct no further tests and make the optimal regulatory decision based on only tier 1 information.

Figure 3.2 illustrates the relationship between the test results to the estimation of human cancer potency. Mutagenicity from tier 1 is highly predictive of whether a chemical is found to be carcinogenic.[9] LD50 from tier 1 has been found to be highly correlated to carcinogenic potency as measured by TD50 for carcinogens.[10-12] Likewise, MTD from tier 2 testing has been found to be highly correlated to TD50.[10,13]

[1] In this analysis we use the Maximum Likelihood Estimate of potency as a proxy for the expected potency that a NBMDM would use to calculate the expected risk.

Most problematic is the relationship between rodent and human carcinogenicity. Previous researchers have used the inter-species concordance between rats and mice as an estimate of human to rodent concordance of bioassay result.[17,18] A similar approach is used in the sensitivity analysis. The NBMDM should choose the testing strategy that yields the highest expected net benefit including testing costs, or equivalently, the strategy that yields the highest net value of information. The VOI net of testing costs is the difference between expected net benefit of optimal regulatory action with information, and the expected net benefit from the optimal regulatory action with only prior information. The optimal level of regulation given an updated expected risk of cancer is based on an evaluation of the benefits to society from cancer cases prevented net of regulatory control costs. The annualized net benefit for each control option k is:

$$NB_k = \frac{\varepsilon_k v \sum_i R_i n_i - c_k}{(1+r)^t} \quad (1)$$

where

- ε_k is the control efficiency for regulatory strategy k (proportion),
- v is the value of a case of cancer prevented (2000 U.S. dollars),
- R_i is the annual risk of cancer to population in exposure group i (probability),
- n_i is the population in exposure group i (persons/year), and
- c_k is the annualized cost of regulatory control (2000 U.S. dollars/year).
- r is the discount rate (percentage), and
- t is the delay in action from testing (years).

The expected net benefit from each testing strategy is the difference of the expected net benefit from the optimal control option and the annualized cost of testing (2000 U.S. dollars).

2.2 Risk Model

We model the lifetime risk of developing cancer using a one-hit model which assumes the risk of tumor is equal to the risk of developing cancer at an unspecified site:

$$1-\exp(-\alpha-\beta d) \tag{2}$$

where

- 1-exp(-α) represents the background tumor rate,
- β is the carcinogenic potency $(mg/kg/day)^{-1}$, and
- d is the dose (mg/kg/day).

The annual risk of cancer above the background level, R, is estimated by dividing the lifetime risk above the background rate by 70 years/lifetime, the approximate human life expectancy:

$$R=\frac{\exp(-\alpha)\left[1-\exp(-\beta d)\right]}{70} \tag{3}$$

Background tumor rates for rodents vary greatly by species, gender and target site. [19] However, most rodent carcinogens (i.e., 92% of mouse carcinogens and 82% of rat carcinogens) can be identified by the eight most common sites.[20] The most common target site for both mice and rats is the liver, followed by the lung in mice and the mammary gland in rats.[20] The background tumor rate for liver adenoma ranges from 0.1% to 9.7% (mean of 3.4%), for various types of lung tumors it ranges from 0% to

0.2% (mean of 0.0%), and for various types of breast tumors it ranges from 0% to 4.5% (mean of 0.8%).[19] In this analysis, we assume that the background tumor rate is 2% for the base case and conduct sensitivity analyses to determine the impact of this assumption.

Prior distribution of carcinogenic potency

In this analysis we assume the uncertainty faced by the NBMDM relates to the true value of carcinogenic potency, β, and the potential results of testing. All other input values are assumed to be known with certainty. The uncertain input values were generated using the random sampling function in S-Plus 2000. Table 3.2 summarizes the parameters for distributions the distributions used to characterize uncertainty.

Similar to the approach used in Taylor et al.[18] and Hammitt and Cave,[21] we model the prior probability of potency as a sum of a probability mass at zero potency (i.e., not a carcinogen) and a continuous parametric distribution for positive potency. Empirical studies show that mutagenicity is a good predictor of whether a chemical will test positive in a bioassay for carcinogenicity. Gold et al.[9] show that of the 465 chemicals in the carcinogenic potency database tested for both mutagenicity in Salmonella and bioassay in rats and mice, 79% of chemicals with positive mutagenicity were found to have positive rodent bioassay results, while 49% of non-mutagens were found to be carcinogenic in bioassays. In this analysis, we assume that a positive mutagenicity test result from tier 1 testing implies a probability of positive potency of 0.8 and a negative mutagenicity test implies a probability of positive potency of 0.5.

Several studies report that although LD50 cannot predict whether a chemical will be a carcinogen, but if a chemical is a rodent carcinogen then a strong empirical

correlation exists between LD50 and potency.[10-12] The most recent analysis by Metzger et al.,[11] based on a data set of 109 chemicals included in the NCI/NTP series with positive test results in rats and mice, showed that the distribution of the log of the ratio of LD50 to TD50 (dose that reduces the proportion of tumor-free animals by 50%):

$$K = \log_{10} \frac{TD_{50}}{LD_{50}} \tag{4}$$

can be estimated by a normal distribution with mean of 0.83 and standard deviation 0.79. For a one-hit model, the potency is related to TD50 by the following equation:[10]

$$\beta = \frac{\ln(2) - \alpha}{TD_{50}} \tag{5}$$

which implies that the natural log of potency will follow a normal distribution, (i.e., positive potency is lognormal).

To estimate the prior distribution of positive potency, we randomly sample 1,000 values from the normal distribution for the ratio in equation (4), and calculate the potency implied by the distribution using the transformation in equation (5). Since the values of positive potency given prior information are randomly generated through Monte Carlo simulation of 1,000 values, the probability of each value is 0.001. Combined with the prior probability of a positive potency provided by the mutagenicity test result:

$$p(\beta = 0) = \begin{cases} 0.2 & mutagen \\ 0.5 & not \end{cases} \tag{6}$$

the probability of any sampled positive value of potency is:

$$p(\beta) = \begin{cases} (0.001)(0.8) & mutagen \\ (0.001)(0.5) & not \end{cases} \tag{7}$$

Posterior distribution given MTD

For predicting possible tier 2 subchronic bioassay results, we use the empirical relationship of LD50 and MTD reported in Gombar et al.[22] for 269 compounds gathered from various databases. From this database, we drop the 12 chemicals where the MTD is greater than LD50, and use @Risk™ version 4.5 (Ref.) to fit distributions to the ratio of MTD to LD50:

$$K = \log_{10} \frac{TD_{50}}{LD_{50}} \tag{8}$$

which yields a lognormal distribution with $\mu_{\ln K} = -2.3$ and $\sigma_{\ln K} = 1.4$ produce a fit with χ^2 statistic of 32 and p-value of 0.01, which implies a good fit. To estimate the distribution of possible MTD results, we randomly sample 1,000 values from the lognormal distribution, and calculate the MTD implied by the ratio.[2]

Crouch et al.[13] analyzed a data set of 213 NCI/NTP rodent bioassays and found that potency is roughly proportional to 1/MTD with a strong correlation ($r_{rat} = 0.91$, $r_{mice} = 0.88$). However, the MTD, like the LD50, is not predictive of whether a chemical will be found to be carcinogenic or not. Taylor et al.[18] used the results of the study to estimate the likelihood of observing a particular MTD given positive potency to be a lognormal distribution with as standard deviation of $\sigma_{\ln y} = 1.2$. Bayesian updating of the potency distribution is calculated using the procedure described by Brand and Small.[23] For positive potencies:

[2] An alternative approach, pursued in the analysis by Taylor et al. (1993), uses the empirical relationship between potency and MTD to predict MTD results given the prior distribution. This approach yields a predicted MTD distribution with similar mean and slightly greater variance than the approach used in this analysis.

$$p(\beta_{i\neq 1} \mid s_j, \beta_i > 0) = \frac{p(\beta_i) L(s_j \mid \beta_i)}{\sum_{k=1}^{1000} p(\beta_k) L(s_j \mid \beta_k)} \tag{9}$$

The input s is the prediction of potency based on the relationship between potency and MTD (R^2=0.84) for 108 mice carcinogens reported in Crouch et al.[13]:

$$\log_{10} s = \log_{10} \frac{1}{MTD} - 0.4 \tag{10}$$

Since MTD is not predictive of whether the chemical is carcinogenic or not, the posterior probability that the chemical is not carcinogenic given any sampled value of MTD is:

$$p(\beta = 0 \mid s) = p(\beta = 0) \tag{11}$$

and the posterior probability of a sampled value β_i given the sampled value s_j is:

$$p(\beta_i \mid s_j) = p(\beta > 0) \frac{p(\beta_i) L(s_j \mid \beta_i)}{\sum_{k=1}^{1000} p(\beta_k) L(s_j \mid \beta_k)} \tag{12}$$

In addition, since s is randomly generated based on the LD50, the unconditional probability of observing s is:

$$h(s_j) = \frac{1}{1000} \tag{13}$$

Posterior distribution given bioassay

The bioassay protocol established by the NCI/NTP requires two species of rodents (rat, mice) – 50 males and 50 females each – to be tested at three dose groups (control, 1/2 MTD, and MTD) from 6 weeks to 24 months of age. For simplicity, in our analysis we consider an ideal type experiment with a single group of animals (50), and

two dose groups (control and MTD), therefore there are 51 possible bioassay results ranging from no animals with tumors to all 50 animals with tumors. Assuming the animal results are probabilistically independent, the likelihood of observing a particular bioassay result follows a binomial distribution. The probability of tumor for the group exposed at the MTD is:

$$p(tumor) = 1 - \exp(-\alpha - \beta MTD) \tag{14}$$

Since the Binomial likelihood is a discrete probability distribution, we can calculate the posterior probability of all 51 possible test results (given a 50 animal test) given a particular MTD test result by the equation:

$$p(\beta_i \mid s_j, x) = \frac{p(\beta_i \mid s_j) L(x \mid \beta_i, s_j)}{\sum_{k=1}^{1001} p(\beta_k \mid s_j) L(x \mid \beta_k, s_j)} \tag{15}$$

where x is the number of animals with a tumor. The denominator represents the distribution of observing x given a particular MTD result:

$$h(x_l \mid s_j) = \sum_{i=1}^{1001} p(\beta_i \mid s_j) L(x_l \mid \beta_i, s_j) \tag{16}$$

Lave et al.[17] argue that observed concordance of bioassays results between mice and rats of 70% can serve as an upper bound for the concordance of carcinogenicity in rodents and humans. Taylor et al.[18] use 70% in their sensitivity analysis and use 100% in their base case analysis. Gold et al. [24] report that of 392 chemicals the carcinogenic potency database tested in both rats and mice, 76% of chemicals that were positive in rats were also positive in mice and 70% of chemicals that were positive in mice were also positive in rats. The data also show that 75% of chemicals that were negative in rats were also negative in mice, and 81% of chemicals that were negative in mice were also negative in

rats. We assume 100% concordance for the base case analysis and compare the result to assuming 75% positive and negative qualitative predictive value of rodent assay. The distribution of potency given positive carcinogenicity is assumed to be the same between rodents and humans.

2.3 Expected value of information

Given the complexity of the problem, we developed a risk model that we solved using simulation in S-Plus 2000™ . Chapter 1 and 2 discuss the evolution and use of Monte Carlo simulation for solving VOI problems, and our methods are consistent with those used by other researchers (See appendix A2 for the complete S-Plus code).[25-27]

The lowest branch in the tree in Figure 3.1 represents taking action based only the prior distribution of potency developed from mutagenicity test result and LD50:

$$E\{NB \mid prior\} = \max_{k}\left[\sum_{i=1}^{1001}(NB_{i,k})p(\beta_i)\right] \tag{17}$$

Here, the NBMDM evaluates the expected net benefit given the prior distribution from each regulatory action and chooses the regulatory action with the highest value.

The middle branch represents a tiered approach where the NBMDM compares the expected net benefit of taking immediate action after an MTD result or the expected net benefit of waiting to collect the bioassay result, and chooses the testing strategy with the higher expected net benefit. The net benefit of taking immediate action after measuring the MTD is:

$$E\{NB \mid MTD\} = \sum_{j=1}^{1000}\left\{\max_{k}\left[\sum_{i=1}^{1001}(NB_{i,k})\,p(\beta_i \mid s_j)\right]\right\}h(s_j) - c_{tier2} \tag{18}$$

Here, the NBMDM chooses the regulatory action that maximizes expected net benefit given the posterior distribution of potency given a particular value of the MTD. The value is calculated for each of the 1,000 different values of the MTD sampled. The net benefit values are averaged over all of the values of the MTD, and the cost of testing is subtracted. The expected net benefit from taking action after collecting the bioassay result is:

$$E\{NB \mid Bio\} = \sum_{j=1}^{1000}\left(\sum_{l=1}^{51}\left\{ \max_{k}\left[\sum_{i=1}^{1001}\left(NB_{i,k}\right)p\left(\beta_i \mid s_j, x_l\right)\right]\right\} h\left(x_l \mid s_j\right)\right) h\left(s_j\right) - c_{tier2} - c_{tier3} \tag{19}$$

Here, the NBMDM chooses the regulatory action that maximizes expected net benefit given the posterior distribution of potency given a particular value of bioassay result and the MTD. The value is calculated for each of the 51 possible bioassay results and 1,000 different values of MTD sampled. The net benefit values are averaged over all of the values of the bioassay and MTD, and the cost of testing is subtracted.

The highest branch represents taking action based on hypothetically available perfect information at no cost and no delay:

$$E\{NB \mid perfect\} = \sum_{i=1}^{1001}\left[\max_{k}\left(NB_{i,k}\right)\right] p\left(\beta_i\right) \tag{20}$$

Here, the NBMDM evaluates the net benefit from each value of potency, and chooses the regulatory action that maximizes the net benefit. The value is then averaged over the prior probability of the potency values.

The difference between the top and bottom branches represents the expected value of perfect information (EVPI), which is the upper bound of the willingness to pay

for reducing uncertainty about potency. The NBMDM, however, must choose a testing strategy that will provide only imperfect information. The net expected value of sample information (EVSI) for the tiered strategy, which accounts for testing cost, is the difference between the expected value of testing and expected value from acting on tier 1 information.

An important property of VOI is that new information must lead a decision maker to change the course of action under some scenarios for the information to be of value. If there is no change in action for any possible information, there are no improvements in welfare. Therefore, if additional information will never change a decision, there is no value in the information from a decision analytic perspective. In addition, since testing is not costless, testing may yield a negative net EVSI (i.e., the "No further testing" strategy has the highest expected net benefit), in which case the NBMDM is better off not doing any testing.

2.4 Four Illustrative Cases

Similar to the approach used by Lave et al.(1988)[17] and Taylor et al.[18] this analysis uses a generic environmental control decision to gain general insights on the value of testing. We determine the optimal testing strategy for four illustrative cases of possible tier 1 testing results:

- Case A: a chemical tests negative in the mutagenicity test, and has relatively low acute toxicity (LD50 of 8000 mg/kg);
- Case B: a chemical tests positive in the mutagenicity test but has a relatively low acute toxicity (LD50 of 8000 mg/kg);

- Case C: a chemical tests negative in the mutagenicity test but has relatively high acute toxicity (LD50 of 60 mg/kg);
- Case D: a chemical tests positive in the mutagenicity test and has a relatively high acute toxicity (LD50 of 60 mg/kg).

Test results of case A imply a lower bound value of expected potency since the chemical is not mutagenic and an LD50 value of 8,000 mg/kg represents roughly the 95th percentile of LD50 values reported in Gombar et al.[22] Similarly, test results of case D imply an upper bound value of expected potency since an LD50 of 60 mg/kg correspond to the 5th percentile of LD50 values.

To keep the calculation general, rather than choosing a particular distribution of exposures for multiple exposure groups, we collapse the information into a measure we call the exposure weighted average dose $\bar{d}$:

$$\bar{d} = \frac{\sum d_i n_i}{N} \tag{21}$$

where N is the sum of all of the populations exposed. Since for each exposure group the annual risk can be estimated as:

$$R_i \approx \exp(-\alpha)\beta d_i / 70 \tag{22}$$

when $\beta d \leq 0.2$, the expected total cases of cancer per year can be estimated by the equation:

$$\sum R_i n_i \approx \bar{R}N = \frac{\exp(-\alpha)\left[1-\exp(-\beta\bar{d})\right]}{70} N \tag{23}$$

where $\bar{R}$ is the exposure weighted average risk of cancer. In this analysis, we vary the possible exposure weighted average dose from 10^{-9} to 1 mg/kg/day. This range

corresponds to the range of average U.S. population exposures to approximately 20 rodent carcinogens for which both concentration and exposure data are available summarized in Table 3.3.[9] We assume that the total population exposed annually is the current U.S. population, which we estimate to be 280 million people.

Table 3.4 summarizes the base case values of constant inputs and the range of values used in the sensitivity analysis. For all cases, we evaluate the VOI for exposure weighted average dose ranging from 10^{-9} to 1 mg/kg/day. For the base case we estimate the value of a cancer prevented to be $7 million in year 2000 dollars to assess the benefit of controlling exposure to the chemical being tested. The $7 million estimate represents the median value from a comprehensive literature review by Viscusi and Aldy[28] of the value of a statistical life (VSL) estimate derived from labor market studies. This value of a cancer case prevented is an overestimate of the true value since it assumes that all cases of cancer are fatal. In a sensitivity analysis, we assess the impact of changing the value to $5 million and $12 million, which represent the first and third quartile, respectively, of the VSL estimates in the labor market studies.

We vary the efficiency of control options from 0% (no regulation) to 99%, and do not explicitly consider the impact of banning a chemical (100% control). In the base case analysis, the NBMDM has three control options: 0%, 50%, and 99%. In sensitivity analysis, we examine the impact of ranging the available options from only two (0% and 99%) to a roughly continuous option of 100 (from 0% to 99% in 1% increments).

We assume quadratic cost function that depends on the parameter "q":

$$c_k = \frac{-\ln(1-\varepsilon_k)}{q} \tag{24}$$

where q is set such that the cost of the 99% control option is $100 million in year 2000 dollars:

$$q = \frac{-\ln(1 - e_{99\%})}{c_{99\%}} \tag{25}$$

We choose $100 million per year in the base case since it represents a threshold considered "economically significant" by federal government.[29] We vary the value from $1 million to $10 billion per year in sensitivity analysis. We use a discount rate of 5% for the base case and 3% and 7% in sensitivity analysis.[30-32] We use EPA's estimates of $200,000 for the one time cost of tier 2 subchronic testing and $1,300,000 for tier 3 long-term bioassay costs, both in year 2000 dollars.[33] The value of information is calculated for a range of values of exposure weighted average dose ($\bar{d}$), regulatory options, costs of control, and dollar value of a cancer case avoided.

3. Results

3.1 Distribution of potency

Figure 3.3A shows the cumulative probability distribution of potency for each of the four cases and the potency distribution for all NTP tests with potency on a log scale. The Tier 1 test results reduce the spread of the potency distribution and a higher toxicity (lower LD50 result) has the effect of shifting the curve to the right (since higher potencies are more probable given higher acute toxicity). A positive mutagenicity result has the effect of shifting down the cumulative distribution curve such that the prior probability of zero potency is 0.2 for a mutagen and 0.5 for a non-mutagen. The expected value of potency for cases A, B, C, and D are 0.0015, 0.0026, 0.21, and 0.30

$(mg/kg/day)^{-1}$ respectively. Figure 3.3B shows the expected annual risk of cancer implied by the prior distribution of potency for the range of doses considered in this analysis both on a log scale. For any given dose, the difference in expected annual cancers between case A and D span over three orders of magnitude.

Figure 3.4 uses the results of case D to illustrate the impact of each level of information collection on the posterior distribution of potency. Figure 3.4A compares the cumulative probability for the prior distribution of potency and the posterior distribution of potency for three values of MTD, the 1st quartile, median, and 3rd quartile of sampled MTD values. As the figure shows, the spread of the distribution becomes much smaller given an MTD result, however, the probability of zero potency remains 0.2 regardless of the MTD result since MTD is not predictive of whether a chemical is carcinogenic. Figure 3.4B compares the cumulative probability for the posterior given the median sampled MTD value, and a bioassay result of no animals with tumors, 1, 2, 3, 4, and 5 animals. Given a non-zero background tumor rate, a zero result in a bioassay will almost certainly imply that the chemical is not a rodent carcinogen. As the number of animals with tumors increase, the probability of zero potency decreases rapidly, and observing 5 animals with tumors (10%) would imply that the chemical has a greater than 95% probability that the potency greater than 0, though the potency is likely to be fairly low.

3.2 Expected value of sample information

The points of indifference between control strategies (the break points) determine the shape and magnitude of the VOI curve as a function of risk. When shifting from one strategy to another, this point occurs where the expected net benefits are equal:

$$\varepsilon_k vRn - c_k = \varepsilon_{k+1} vRn - c_{k+1} \tag{26}$$

where ε_k and c_k is the control efficiency and control cost of control option k, and k+1 is the next more stringent level of control available. Therefore, the breakpoint risk is:

$$R^* = \frac{c_{k+1} - c_k}{(\varepsilon_{k+1} - \varepsilon_k) vn} \tag{27}$$

The breakpoint risk is the same for all four cases because it depends only on the ratio of control costs to the value placed on the cancer cases prevented. However, the breakpoint dose differs since the expected value of potency is different across cases. Given our model for risk in equation (3), the breakpoint dose is:

$$d^* = \frac{\ln\left[R^*(-70) + \exp(-\alpha)\right] + \alpha}{-\beta} \tag{28}$$

For the four cases, these values are given in Table 3.5.

Figure 3.5 shows the (A) optimal control decision without further testing and (B) value of tiered testing net of testing costs for all cases plotted against exposure weighted average dose. The first plot shows the breakpoints where the optimal prior strategy switches from no control to 50% control and then from 50% control to 99% control for all four cases. As the second plot shows, since we assume a quadratic cost function, the leap from 50% to 99% determines the main peak of the VOI curves, though a small peak exists for the transition from 0% to 50% control. The range of exposures for which value of tiered testing is positive spans roughly two orders of magnitude for each of the cases, though the range is slightly smaller for mutagens (Cases B and D). When exposure is very low, the optimal decision is always no control, no matter how high the carcinogenic potency; therefore, the value of information is zero or close to zero. Similarly, when exposure is very high, the negative consequence of not controlling a carcinogen are so

high that optimal action after testing rarely deviates from the optimal action without testing of 99% control. Since the bioassay cannot perfectly predict whether a chemical is a carcinogen or not, the value of imperfect information approach zeroes. Furthermore, by delaying the action until both tier 2 and tier 3 test results are evaluated, there are foregone benefits that increase proportionally to the level of exposure.

Figure 3.6 (A) shows the value of information net of testing and delay costs for case D with the base case assumptions from two information collection scenarios described in Figure 3.1: availability of hypothetical perfect information without cost and the tiered approach. Both reach their maximum at the breakpoint between 50% and 99% control, though a slight peak can be seen at the breakpoint between no control and 50%. In the case of perfect information, given the assumption of 20% probability that the chemical is not a carcinogen, obtaining perfect information prevents unnecessarily spending $100 million in control costs 20% of the time. Panel B shows the discounted expected cost savings for Case D, and Panel C shows discounted expected cases of cancers prevented from tiered testing. As the panels show, to the left of the main breakpoint, the net EVSI is driven by reducing regulatory false negatives; with additional information from the MTD and bioassay, the NBMDM switches from 50% to 99% control in some cases, thereby preventing more cancers, but at a higher cost. To the right of the breakpoint, regulatory false positives are reduced such that the NBMDM prevents fewer cancers but saves control costs by switching from 99% to 50% in some cases. However, greater the dose, the higher the probability that 99% is the optimal choice even with additional information so the cost savings decrease. The foregone benefits from waiting to act drive

3.3 Optimal Testing Strategy

NBMDM should conduct Tier 2 testing for the range of exposures where the net value of tiered testing is positive. Given the three control options, the costs of control, and the value of per cancer case avoided, all the NBMDM needs to know is whether the average dose is within that range. Figure 3.8 reports the optimal testing strategy given Tier 1 as a function of dose and cost of 99% regulatory control for cases A and D.[3] Between the two extreme cases, there is a shift in the no control vs. testing frontier to the right about two orders of magnitude along the dose axis, but the general story is similar. For both cases A and D, over a range of exposure weighted average doses, the cost of control matters in the decision to conduct further testing. Furthermore, even with the assumption that rodent bioassays are 100% concordant with human carcinogenicity and for the most extreme case (i.e., case D, which represents an "upper bound" for potential Tier 1 results), Tier 2 testing is not optimal for a range of plausible doses and control costs. If we assume that the chemicals in the Table 3.3 represents a random distribution of possible levels of average environmental exposures, a group of non-mutagenic chemicals with low toxicity, at the base case level of $100 million per year in control costs, doing nothing (no testing, no control) would be the optimal action for about three quarters of the chemicals. Even for mutagenic chemicals with high toxicity, the optimal action would be no further action for about a third of the chemicals. For another third the optimal strategy would be to control at 99% without any further testing.

---

[3] Contour plot for case A is very similar to the plot for case B, except case B contains a small area in the bottom right section where 99% control is optimal. The plot for case C is very similar to the plot for case D, with a slightly smaller area in the bottom right where 99% control is optimal.

3.4 Sensitivity Analysis

Table 3.7 reports the sensitivity of the break point dose for optimal testing decision to discount rate, value of cancer prevented, qualitative discordance, number of control options and background tumor rate for Case D at three cost levels of 99% control: $1 million, $100 million, and $10 billion. Lowering the discount rate reduces the annualized testing costs and the foregone benefits from waiting to act such that it increases the net EVSI. The decision to control nothing vs. tiered testing is essentially insensitive to the discount rate since the differences in the net EVSI are due mainly to the effect of the discount rate on the annualization of direct testing costs. On the other hand, for the decision to do tiered testing vs. controlling at 99%, lowering the discount rate reduces the cost of delay such that the breakpoint is reached at a higher dose (i.e., testing is optimal for a larger range of exposure values).

In contrast, the impact of different values for preventing cancer on net EVSI is less predictable since it affects both the expected net benefit given testing information and the expected net benefit given only prior information. Figure 3.8 shows the sensitivity of the optimal control decision without further testing and net EVSI to value of a cancer case prevented when control costs are $100 million. Since increasing the value for cancer prevented shifts the breakpoint dose of the optimal control decision without further testing to the left, it shifts the EVSI curves to the left as well. Therefore, as the values in Table 3.7 shows, higher VSL shifts the cut-off exposure weighted average dose to a lower value while lower VSL shifts the cut-off to a higher value.

In the base case analysis we assumed 100% concordance between rodents and human carcinogenicity, which overstates the value of bioassay. Assuming a 75% concordance between rodents and humans reduces the EVSI and narrows the range of exposures for which testing Tier 2 is optimal. Increasing the number of control options has an ambiguous effect on the cut-off doses for testing vs. stopping, but the changes are relatively small. The optimal testing decision is also relatively insensitive to changes in the background tumor rate. In general it appears that although the magnitude net EVSI may vary somewhat depending on the assumptions about discount rate, VSL, and number of available control options, the range of exposures for which tiered testing is optimal is fairly stable. In other words, Figure 3.7 is not sensitive to these parameters.

We also evaluate the impact of choosing to sample 1,000 values for potency, by repeating the analysis for ten different random seeds. Table 3.8 reports the EVSI for four different dose levels and the break point dose for the decision to no control versus test Tier 2 and test Tier 2 versus 99% control for 10 different iterations along with the mean and standard deviation of the 10 iterations, and an estimate of the 95% confidence interval for the mean of the iterations. Though the EVSI estimates vary somewhat, with the spread increasing with higher levels of exposure, the break point dose of whether to test Tier 1 or not is fairly consistent.

4. Discussion

How should EPA determine whether currently available information is "adequate" to assess potential risks to children? Collecting additional information will assist in refining the risk estimate, but perfect information can never be collected. How much

should uncertainty about risk be reduced before action is taken? This paper has argued that an important criterion for making that determination is whether additional information would assist in making better risk management decisions to improve overall societal welfare. It shows that both the level of expected human exposure weighted average dose and economic considerations such as control costs for reducing exposure matter in the decision to pursue further testing. The analysis shows that if the exposure level is low enough and control costs are high enough, then gathering information beyond Tier 1 screening tests is not optimal, since the additional information would rarely indicate that controlling exposure is necessary. In contrast, since we assume that the decision maker is able to regulate through analogy (i.e., regulate a chemical as a carcinogen based on results from Tier 1 results), if the exposure is high enough and control costs low enough, maximum control should be implemented without Tier 2 testing. These observations hold over plausible exposure and cost ranges for both of the two extreme cases of Tier 1 test results. Sensitivity analysis showed that factors such as the value placed on a cancer case prevented and discount rate are not as critical to the decision.

Fortunately, the VCCEP structure recognizes the importance of exposure information and simultaneously including screening level exposure information in Tier 1 to derive a "conservative" estimate of exposure to children or perspective parents. This type of bounding exercise can help determine whether exposure to a chemical is within the range where further testing is beneficial. Alternatively, simple measures of exposure based on an estimate of exposure efficiency or intake fraction – the fraction of a chemical released that is eventually inhaled or ingested – can be used to estimate whether

or not the exposure crosses the threshold where Tier 2 testing is desirable, since it "may be used in risk assessments without introducing appreciable uncertainty".[34] On the other hand, the VCCEP does not collect "screening" level assessments of potential risk reduction opportunities, or any information about their likely effectiveness or costs of implementation. This information is important for the "middle" range of exposure levels where the decision to continue to test or not depends on the cost and effectiveness of control.

Though the analysis provides some interesting policy insights, there are important limitations to the results and many potential important refinements. For example, since we assume in the base case perfect concordance between the rodent bioassay result and human carcinogenicity we are greatly overstating the value of animal testing. The sensitivity analysis using mouse to rat qualitative discordance as a proxy for human to rodent discordance shows that there is a decrease in the dose ranges for which further testing is optimal when imperfect concordance is factored in. Our analysis also ignores the animal welfare concerns, and the latency of cancer. In addition, the predictive value of lower tier tests in estimating carcinogenic potency relies on historical data that may not accurately reflect the distribution of test results for the untested chemicals.

In addition, we assume that the decision maker is able to regulate based on lowered tiered tests without a bioassay result. However, for chemicals already in use, the current regulatory structure does not ordinarily allow for regulation of a chemical as a carcinogen without either bioassay results or human epidemiological results. To the extent that the NBMDM is constrained by the necessity of a test result to regulate, the value of testing will increase. In addition, decision makers are often constrained by

statutory requirements such that maximizing net benefit is not the only criterion for taking regulatory action. How much these constraints change the decision to test or not will be explored in the following chapter. Another important area for future research is further exploration of whether more generic information (i.e., not chemical specific) such as animal to human concordance of test results and correlation between toxicity tests is more valuable than additional toxicity data for particular chemicals. In other words, are research efforts to refine our understanding of relationships between chemicals more valuable than a testing program like VCCEP that is geared towards gathering chemical-specific information?

The VCCEP treats the decision to require higher tier tests as a purely scientific assessment, however, the decision to continue testing is a risk management decision that may have significant impacts on health as well as regulatory costs. The peer consultation required after each tier of testing is in the spirit of an important National Research Council (NRC) recommendation that risk characterization be an "analytic-deliberative" process where interested parties have an opportunity to exchange views and interpretations of the analyses. However, it falls short of the NRC's recommendation that risk characterization be a "decision-driven activity directed towards informing choices and solving problems."[35:155] The information requirement of a formal VOI analysis may be too onerous for many chemicals, however, the general insights gained from these illustrative cases may provide some guidance on appropriate action. Though decision analytic tools such as VOI can never provide a definitive answer on appropriate actions, as this analysis illustrates, it can serve as an important input to the deliberative decision-making process developed for the VCCEP program.

References

1. David Roe, William Pease, Karen Florini et al., "Toxic Ignorance," (Environmental Defense, New York, NY, 1997).

2. U.S. Environmental Protection Agency, "Chemical Hazard Data Availability Study: What Do We Really Know About the Safety of High Production Volume Chemicals?" (Office of Pollution Prevention and Toxics, Washington, DC, 1998).

3. Organisation for Economic Co-operation and Development, "Screening Information Data Set (SIDS) Manual," (OECD Programme on the Co-operative Investigation of High Production Volume Chemicals, 1997).

4. U.S. Environmental Protection Agency, "Testing of Certain High Production Volume Chemicals," *Federal Register*, 65(248), 81658-81685 (2000).

5. U.S. President, "Executive Order 13045 - Protection of Children From Environmental Health Risks and Safety Risks," *Federal Register*, 62(78), 19885-19888 (1997).

6. U.S. Environmental Protection Agency, "Voluntary Children's Chemical Evaluation Program," *Federal Register*, 65(248), 81700-81718 (2000).

7. National Research Council, *Toxicity Testing: Strategies to Determine Needs and Priorities* (National Academy Press, Washington, DC, 1984).

8. R. A. Howard, "Information Value Theory," *IEEE Transactions on Systems Science and Cybernetics*, SSC2(1), 22-26 (1966).

9. L. S. Gold, T. H. Slone, and B. N. Ames, "What do animal cancer tests tell us about human cancer risk? Overview of analyses of the carcinogenic potency database," *Drug Metabolism Reviews*, 30(2), 359-404 (1998).

10. D. Krewski, D. W. Gaylor, A. P. Soms et al., "An Overview of the Report - Correlation between Carcinogenic Potency and the Maximum Tolerated Dose - Implications for Risk Assessment," *Risk Analysis*, 13(4), 383-398 (1993).

11. B. Metzger, E. Crouch, and R. Wilson, "On the Relationship between Carcinogenicity and Acute Toxicity," *Risk Analysis*, 9(2), 169-177 (1989).

12. L. Zeise, E. A. C. Crouch, and R. Wilson, "A Possible Relationship between Toxicity and Carcinogenicity," *Journal of the American College of Toxicology*, 5(2), 137-151 (1986).

13. E. Crouch, R. Wilson, and L. Zeise, "Tautology or Not Tautology," *Journal of Toxicology and Environmental Health*, 20(1-2), 1-10 (1987).

14. D. W. Layton, B. J. Mallon, D. H. Rosenblatt et al., "Deriving Allowable Daily Intakes for Systemic Toxicants Lacking Chronic Toxicity Data," *Regulatory Toxicology and Pharmacology*, 7(1), 96-112 (1987).

15. L. B. Lave and G. S. Omenn, "Cost-Effectiveness of Short-Term Tests for Carcinogenicity," *Nature*, 324(6092), 29-34 (1986).

16. L. B. Lave and G. S. Omenn, "Screening Toxic-Chemicals - How Accurate Must Tests Be," *Journal of the American College of Toxicology*, 7(5), 565-574 (1988).

17. L. B. Lave, F. K. Ennever, H. S. Rosenkranz et al., "Information Value of the Rodent Bioassay," *Nature*, 336(6200), 631-633 (1988).

18. A. C. Taylor, J. S. Evans, and T. E. McKone, "The Value of Animal Test Information in Environmental-Control Decisions," *Risk Analysis*, 13(4), 403-412 (1993).

19. I. Linkov, R. Wilson, and G. M. Gray, "Anticarcinogenic responses in rodent cancer bioassays are not explained by random effects," *Toxicological Sciences*, 43(1), 1-9 (1998).

20. L. S. Gold, N. B. Manley, T. H. Slone et al., "Compendium of chemical carcinogens by target organ: Results of chronic bioassays in rats, mice, hamsters, dogs, and monkeys," *Toxicologic Pathology*, 29(6), 639-652 (2001).

21. J. K. Hammitt and J.A.K Cave, "Research Planning for Food Safety: A Value of Information Approach", R-3946-ASPE/NCTR, (1991).

22. V. K. Gombar, K. Enslein, J. B. Hart et al., "Estimation of Maximum Tolerated Dose for Long-Term Bioassays from Acute Lethal Dose and Structure by Qsar," *Risk Analysis*, 11(3), 509-517 (1991).

23. K. P. Brand and M. J. Small, "Updating uncertainty in an integrated risk assessment: Conceptual framework and methods," *Risk Analysis*, 15(6), 719-731 (1995).

24. L. S. Gold, L. Bernstein, R. Magaw et al., "Interspecies Extrapolation in Carcinogenesis - Prediction between Rats and Mice," *Environmental Health Perspectives*, 81, 211-219 (1989).

25. M. E. Dakins, J. E. Toll, and M. J. Small, "Risk-Based Environmental Remediation - Decision Framework and Role of Uncertainty," *Environmental Toxicology and Chemistry*, 13(12), 1907-1915 (1994).

26. M. E. Dakins, J. E. Toll, M. J. Small et al., "Risk-based environmental remediation: Bayesian Monte Carlo analysis and the expected value of sample information," *Risk Analysis*, 16(1), 67-79 (1996).

27. K. M. Thompson and J. S. Evans, "The value of improved national exposure information for perchloroethylene (Perc): A case study for dry cleaners," *Risk Analysis*, 17(2), 253-271 (1997).

28. W. Kip Viscusi and JE Aldy, "The Value of a Statistical Life: A Critical Review of Market Estimates throughout the World", Discussion Paper No. 392, (2002). Available at: http://www.law.harvard.edu/programs/olin_center/papers/392_viscusi.htm

29. U.S. President, "Executive Order 12866 - Regulatory Planning and Review," *Federal Register*, 58(190), 51734-51744 (1993).

30. Robert W. Hahn, "Regulatory Reform: What Do the Government's Numbers Tell Us?," in *Risk, Costs, and Lives Saved: Getting Better Results from Regulation*, edited by Robert W. Hahn (Oxford University Press, The AEI Press, Washington, DC, 1996).

31. M. C. Weinstein, J. E. Siegel, M. R. Gold et al., "Recommendations of the panel on cost-effectiveness in health and medicine," *Jama-Journal of the American Medical Association*, 276(15), 1253-1258 (1996).

32. Office of Management and Budget, "Economic Analysis of Federal Regulations Under Executive Order 12866", (1996). Available at: http://www.whitehouse.gov/omb/inforeg/riaguide.html

33. U.S. Environmental Protection Agency, "Supporting Statement for a Request for OMB Review under the Paperwork Reduction Act", OPPT-2002-0005-0002, (2002).

34. J. S. Evans, K. M. Thompson, and D. Hattis, "Exposure efficiency: Concept and application to perchloroethylene exposure from dry cleaners," *Journal of the Air & Waste Management Association*, 50(9), 1700-1703 (2000).

35. National Research Council, *Understanding Risk: Informing Decisions in a Democratic Society* (National Academy Press, Washington, DC, 1996).

Tables and Figures

Table 3.1: Testing Tiers of the VCCEP

Tier	Test[6]	Information	Estimated Cost[33] (2000 dollars)
1	Acute oral toxicity (up/down) OR	LD_{50}	-
	Acute inhalation toxicity		$14,735
	In vitro gene mutation: Bacterial reverse mutation assay	Qualitative	$7,389
	Repeated dose toxicity with reproductive and developmental toxicity screens OR	NOAEL	$40,630
	Repeated dose oral toxicity AND Reproductive toxicity (1-generation)		-
	In vitro chromosomal aberrations OR *In vivo* chromosomal aberrations OR	Qualitative	-
	In vivo mammalian erythrocyte micronucleus		$15,158
2	90-Day subchronic toxicity in rodents (oral; inhalation)	MTD, NOAEL	$105,214; $305,507
	Reproduction and fertility effects	NOAEL	$826,676
	Prenatal developmental toxicity (two species)	NOAEL	$88,448
	In vivo mammalian bone marrow chromosomal aberrations, OR	Qualitative	-
	In vivo mammalian erythrocyte micronucleus		$15,158
	Immunotoxicity	NOAEL	$45,887
	Metabolism and pharmacokinetics	Qualitative	$31,650
3	Carcinogenicity OR	Potency, NOAEL	$1,259,677
	Chronic toxicity/carcinogenicity		-
	Neurotoxicity screening battery	NOAEL	$100,001
	Developmental neurotoxicity	NOAEL	$168,212

Figure 3.1: Simplified schematic of the testing decision

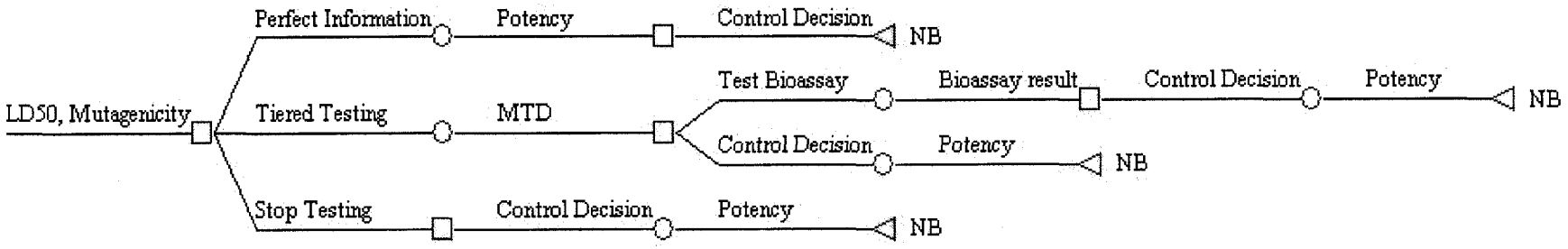

Figure 3.2: Relationship between testing results and human carcinogenic potency

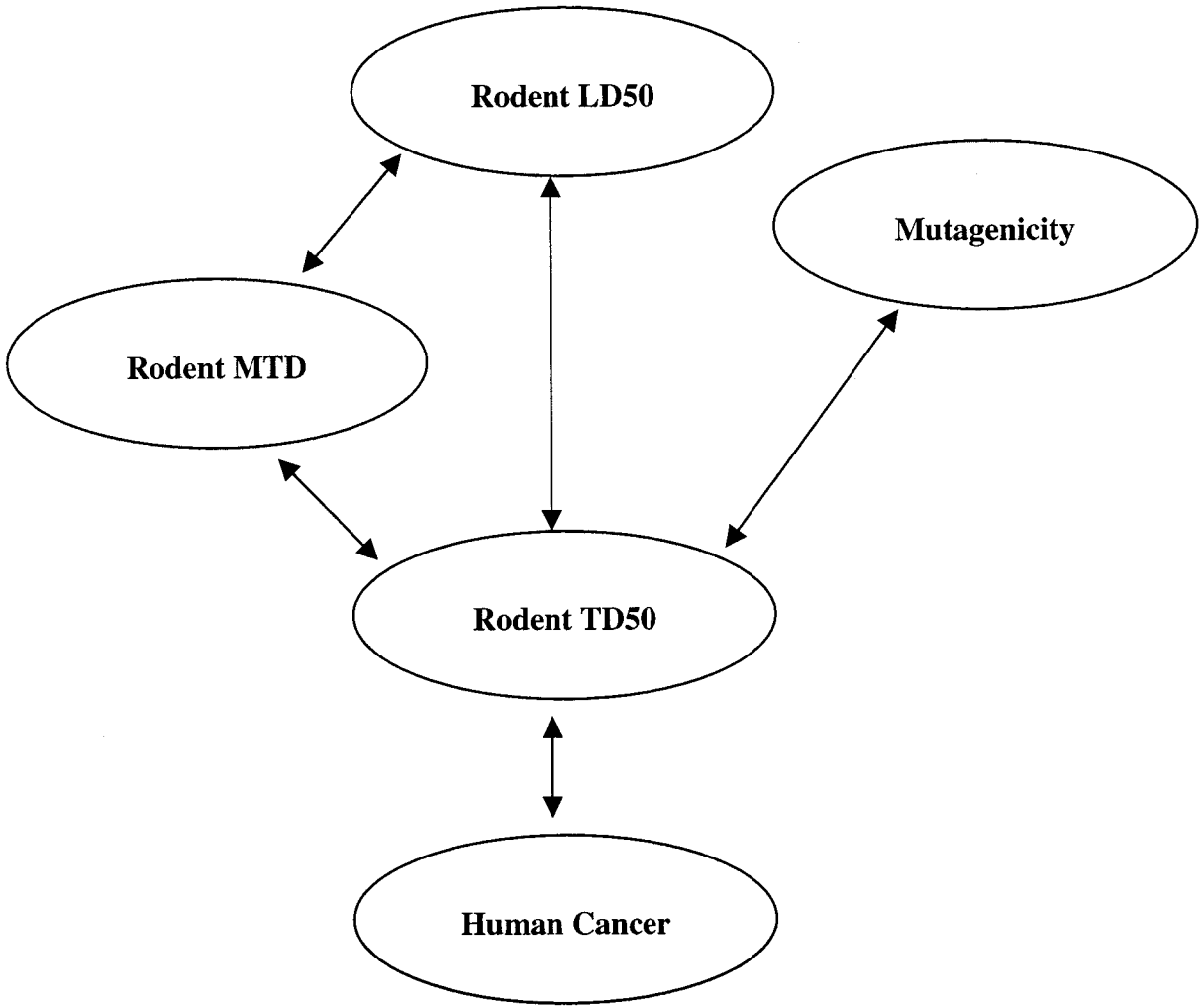

Table 3.2: Parameters for uncertain input values

Input	Distribution	Parameter	Value	Reference
Background tumor rate	-	1-exp(-α)	0.02	Linkov et al.[19]
Predictive value: $P(\beta > 0 \mid Mut+)$	Probability mass		0.8	Gold et al.[9]
Predictive value: $P(\beta > 0 \mid Mut-)$	Probability mass		0.5	Gold et al.[9]
Ratio: $K = \log 10 \frac{TD50}{LD50}$	Normal	μ_K	0.83	Metzger et al.[11]
		σ_K	0.79	
Ratio: $K = \frac{MTD}{LD50}$	Lognormal	$\mu_{\ln K}$	-2.3	Gombar et al.[22]
		$\sigma_{\ln K}$	1.4	
Likelihood: $L\left(\frac{1}{MTD} \mid \beta\right)$	Lognormal	$\mu_{\ln y}$	$\ln \beta - \frac{\sigma^2_{\ln y}}{2}$	Taylor et al.[18]
		$\sigma_{\ln y}$	1.2	
Predictive value: $P(\beta_{human} > 0 \mid \beta_{rodent} > 0)$	Probability mass		0.75	Gold et al.[24]
Predictive value: $P(\beta_{human} = 0 \mid \beta_{rodent} = 0)$	Probability mass		0.75	Gold et al.[24]

Table 3.3: Estimates of U.S. Average Daily Dose to Rodent Carcinogens

Rodent Carcinogen	Dose (mg/day)	Dose (mg/kg/day)[4]
TCDD (1994)	1.2×10^{-8}	1.7×10^{-10}
Chlorobenzilate (1989)	6.4×10^{-6}	9.1×10^{-8}
Chlorothalonil (1990)	6.4×10^{-6}	9.1×10^{-8}
Folpet (1990)	1.3×10^{-5}	1.8×10^{-7}
Aflatoxin (1984-89)	1.8×10^{-5}	2.6×10^{-7}
PCNB (1990)	1.9×10^{-5}	2.7×10^{-7}
Lindane (1990)	3.2×10^{-5}	4.6×10^{-7}
PCBs (1984-86)	9.8×10^{-5}	1.4×10^{-6}
Captan (1990)	1.2×10^{-4}	1.6×10^{-6}
EDB (before 1984 ban)	4.2×10^{-4}	6.0×10^{-6}
Dicofol (1990)	5.4×10^{-4}	7.8×10^{-6}
Toxaphene (1990)	6.0×10^{-4}	8.5×10^{-6}
DDE/DDT (1990)	6.6×10^{-4}	9.4×10^{-6}
Carbaryl (1990)	2.6×10^{-3}	3.7×10^{-5}
UDMH (1988)	2.8×10^{-3}	4.0×10^{-5}
DDE (before 1972 ban)	6.9×10^{-3}	9.9×10^{-5}
Ethylene thiourea (1990)	9.5×10^{-3}	1.4×10^{-4}
DDT (before 1972 ban)	1.4×10^{-2}	2.0×10^{-4}
BHA (1987)	7.0×10^{-1}	1.0×10^{-2}
Saccharin (1977)	7.0×10^{0}	1.0×10^{-1}

Source: Gold et al. [9]

[4] Dose per 70-kg individual

Table 3.4: Constant input values

Input	Symbol	Base Case	Sensitivity	Units	Source
Exposure weighted average population dose	d	-	10^{-9} to 10^{-1}	mg/kg/day	Gold et al. [9]
Value of cancer prevented	v	\$7 million	\$5 million, \$12 million	2000 dollars per statistical life	Viscusi and Aldy[28]
Efficiency of control k	e_k	0%, 50%, 99%	0%, 99%; 0%, 1%, 2%, ..., 99%	percentage	Hypothetical
Cost of 99% control	$c_{99\%}$	\$100 million	\$1 million to \$10 billion	2000 dollar per year	Hypothetical
Discount rate	r	5%	3%, 7%	percentage	Hahn[30], OMB[32], Weinstein et al.[31]
Cost of tier 2 testing	c_{tier2}	\$200,000r		2000 dollars per year	U.S. EPA[33]
Cost of tier 3 testing	c_{tier3}	\$1,300,000r		2000 dollars per year	U.S. EPA[33]

Figure 3.3: Prior distribution of potency and expected annual cases of cancer (Cases A, B, C, and D)

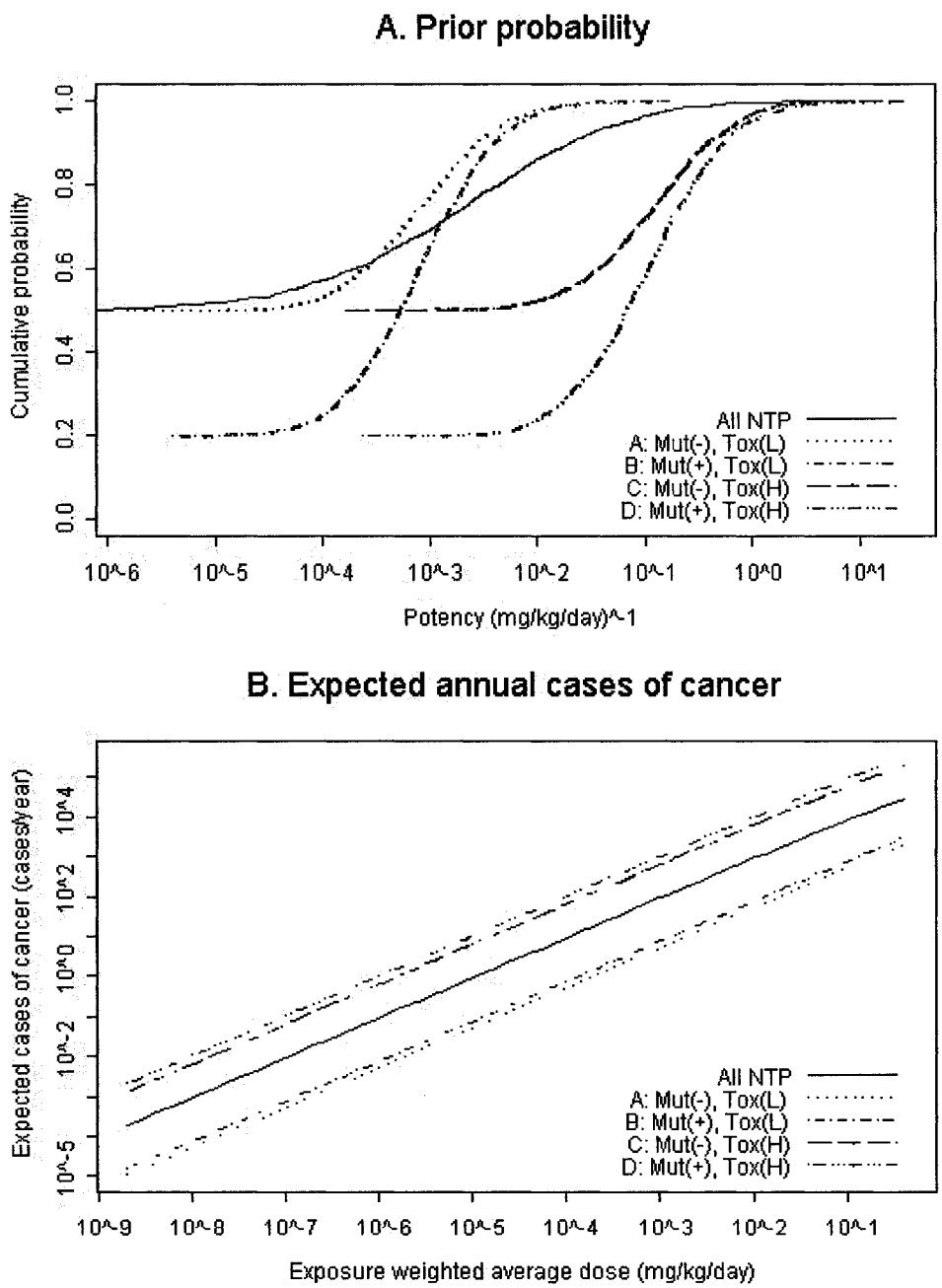

Figure 3.4: Posterior distribution of potency (Case D)

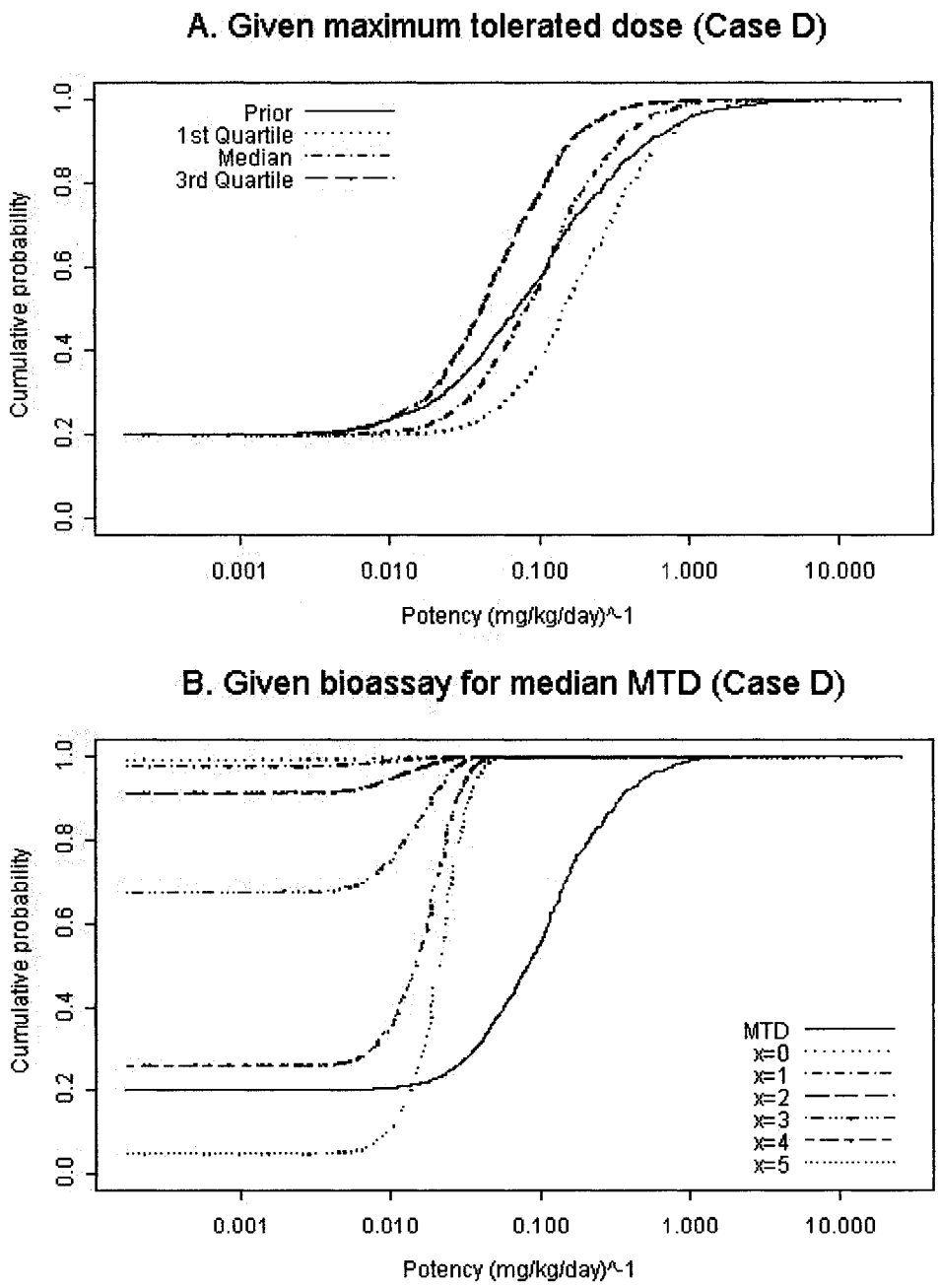

Table 3.5: Break point dose of optimal control strategy without further testing (Cases A, B, C, and D)

Control strategies	R^*	*Break point dose (mg/kg/day)*			
		Case A	*Case B*	*Case C*	*Case D*
0% vs. 50%	1.5×10^{-8}	7.3×10^{-4}	4.3×10^{-4}	5.2×10^{-6}	3.6×10^{-6}
50% vs. 99%	8.8×10^{-8}	4.2×10^{-3}	2.5×10^{-3}	3.0×10^{-5}	2.1×10^{-5}

Figure 3.5: Optimal control decision without further testing and expected value of information net of testing and delay costs

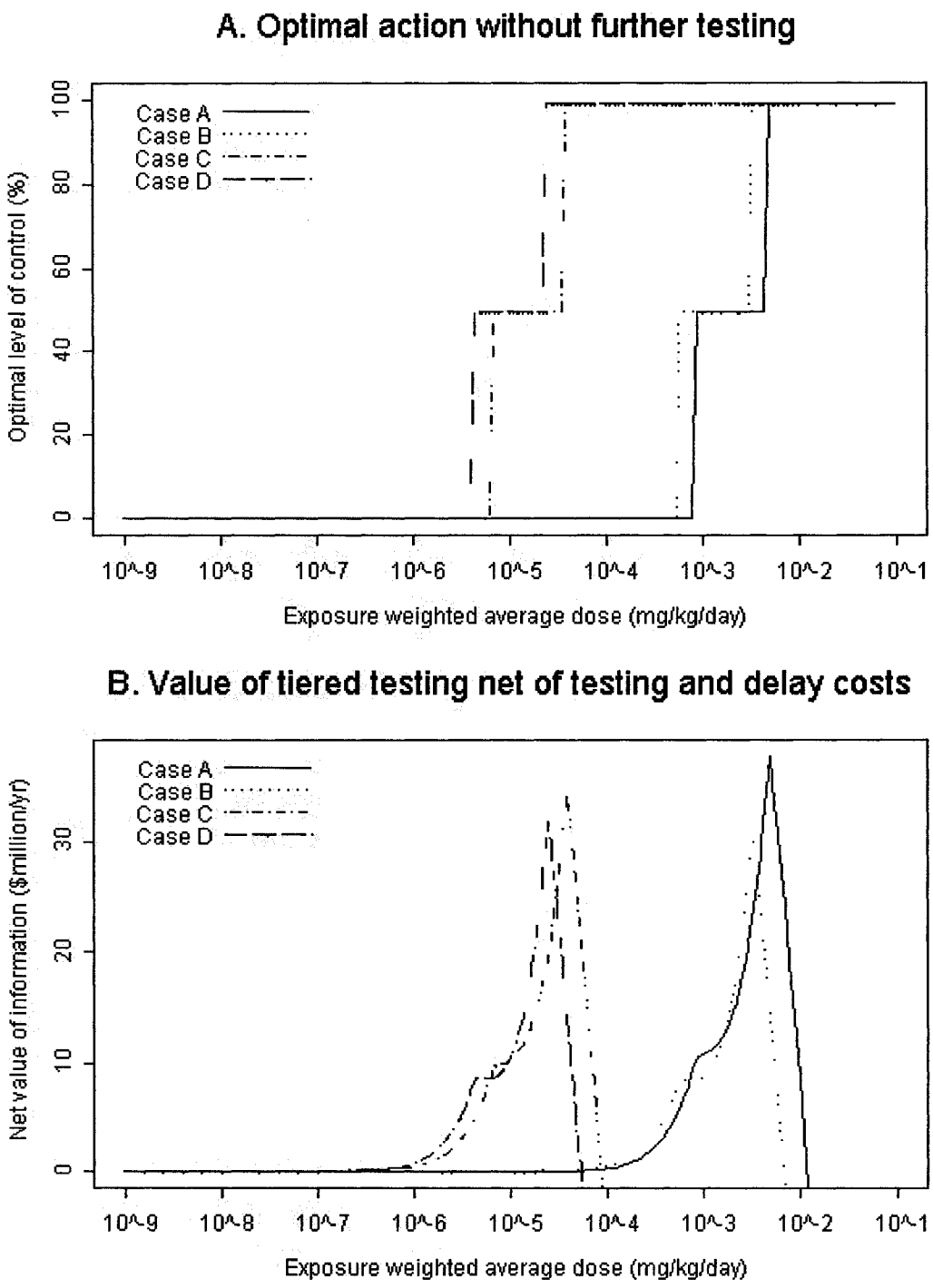

Figure 3.6: Expected value of information net of testing and delay costs, control cost saved and cancers prevented from tiered testing (Case D)

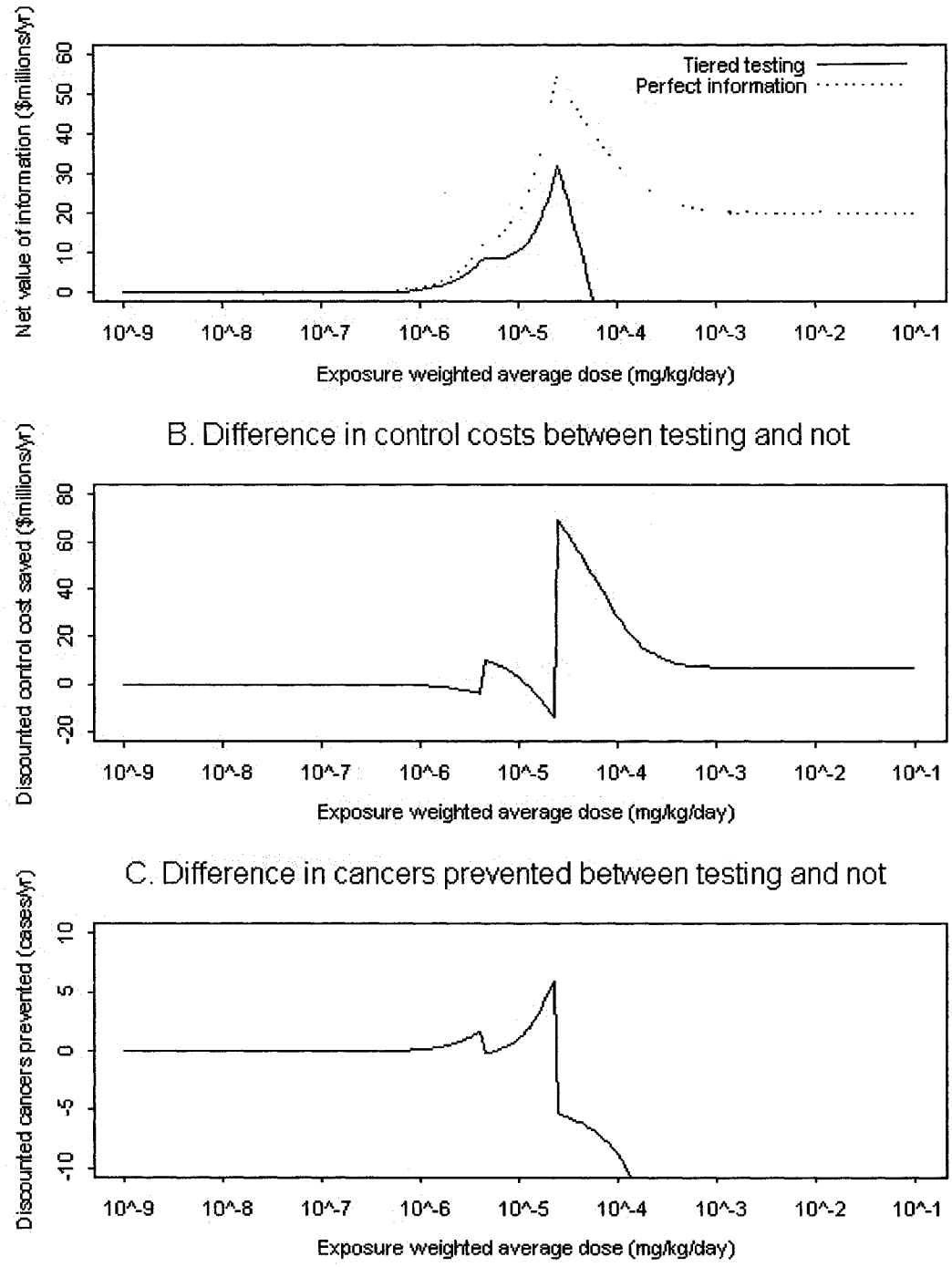

Figure 3.7: Optimal testing decision given tier 1 result as a function of control cost and exposure (Cases A and D)

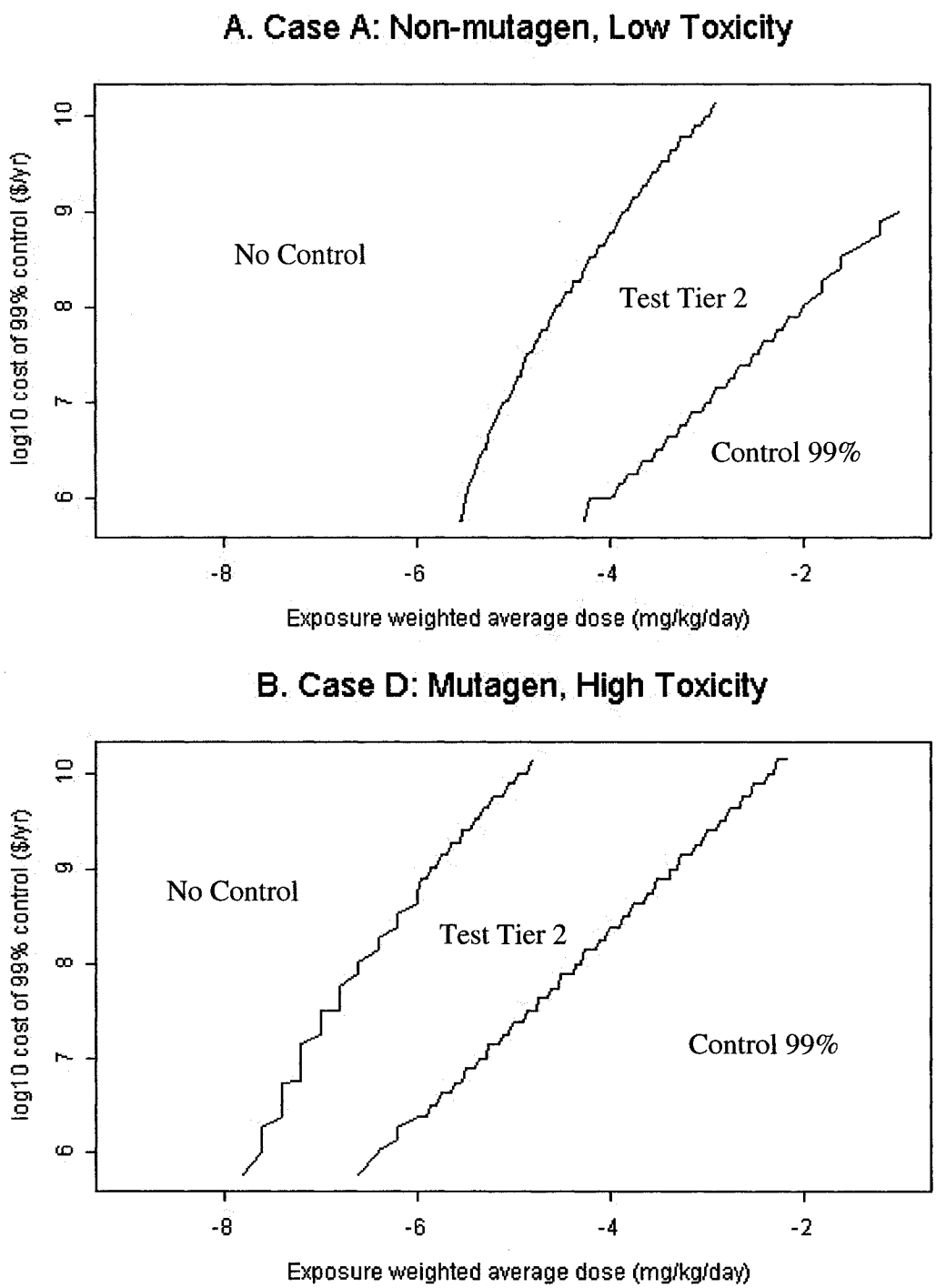

Table 3.6: Sensitivity of the break point dose for optimal testing decision to discount rate, value of cancer prevented, qualitative discordance, number of control options and background tumor rate (case D)

	0% Control vs. Test Tier 2			*Test Tier 2 vs. Control 99%*		
Cost of 99% control	***$1 million***	***$100 million***	***$10 billion***	***$1 million***	***$100 million***	***$10 billion***
Base Case	2E-08	2E-07	2E-06	4E-07	5E-05	8E-04
Discount Rate = 7%	2E-08	2E-07	2E-06	4E-07	4E-05	7E-04
Discount Rate = 3%	1E-08	2E-07	2E-06	6E-07	7E-05	1E-03
VSL = $12 million	1E-08	1E-07	2E-06	3E-07	3E-05	2E-04
VSL = $5 million	2E-08	3E-07	2E-06	6E-07	7E-05	7E-05
Qualitative Discordance = 75%	3E-08	2E-07	2E-06	6E-07	7E-05	1E-03
2 Control Options	-	4E-07	-	-	8E-05	-
100 Control Options	-	2E-07	-	-	6E-05	-
Background Tumor = 0%	-	2E-07	-	-	5E-05	-
Background Tumor = 10%	-	2E-07	-	-	6E-05	-

Figure 3.8: Sensitivity of optimal control decision without further testing and net EVSI to value of a cancer case prevented (Case D)

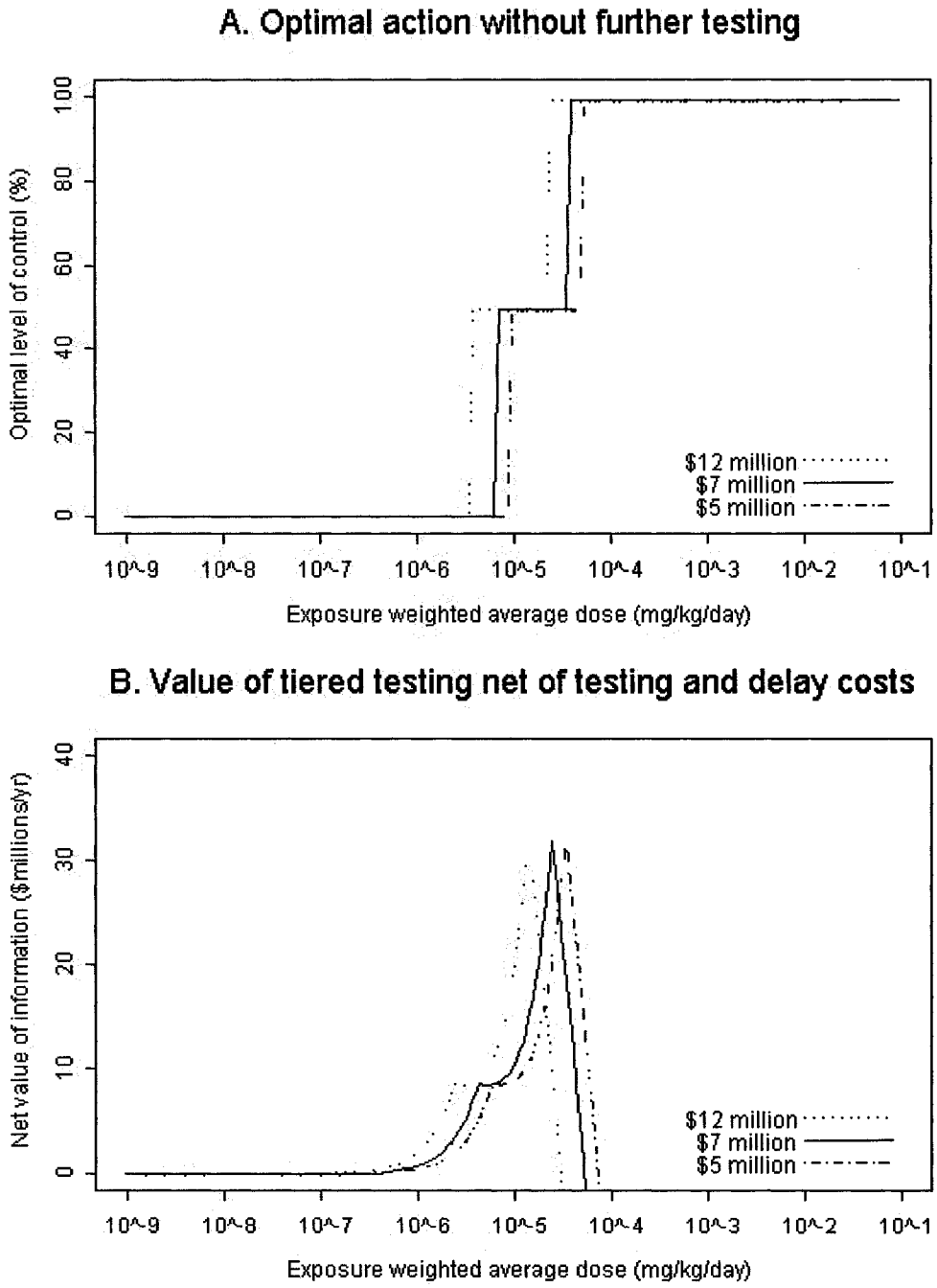

Table 3.7: Sensitivity of the value of testing and the break point dose for optimal testing decision to random seed (case D)

	Expected value of testing ($ millions)				Break Point Dose (mg/kg/day)	
	Dose (mg/kg/day)					
	1.00E-07	*1.00E-06*	*1.00E-05*	*1.00E-04*	*0% Control vs. Test Tier 2*	*Test Tier 2 vs. Control 99%*
Iteration 1	-$0.010	$0.59	$10.0	-$29.5	2.0E-07	5.5E-05
Iteration 2	-$0.010	$0.18	$5.8	-$19.8	3.5E-07	6.0E-05
Iteration 3	-$0.010	$0.32	$7.6	-$21.1	2.0E-07	6.0E-05
Iteration 4	-$0.010	$0.29	$7.4	-$21.9	2.5E-07	6.0E-05
Iteration 5	-$0.010	$0.37	$7.9	-$24.7	2.0E-07	6.0E-05
Iteration 6	-$0.008	$0.53	$8.7	-$30.0	1.5E-07	5.5E-05
Iteration 7	-$0.010	$0.33	$7.7	-$24.0	3.0E-07	6.0E-05
Iteration 8	-$0.009	$0.40	$8.5	-$22.8	2.0E-07	6.0E-05
Iteration 9	-$0.010	$0.28	$7.0	-$21.2	3.0E-07	6.0E-05
Iteration 10	-$0.009	$0.59	$9.4	-$26.2	1.5E-07	5.5E-05
Mean	-$0.010	$1.55	$2.4	-$52.7	2.3E-07	5.9E-05
Std Dev	$0.000	$0.39	$0.5	$5.3	6.7E-08	2.4E-06
95% lower confidence limit of mean	-$0.010	$1.27	$2.0	-$56.5	1.8E-07	5.7E-05
95% upper confidence limit of mean	-$0.010	$1.83	$2.7	-$48.9	2.8E-07	6.0E-05

Appendix

Selected S-Plus code for evaluating the value of information and optimal testing strategies

```
# clear all previous data objects
  remove(ls())

# ==========================================
# Assign values to constants for the base case
# ==========================================

  n.b <- 1000                       # number of beta to sample
  n.s <- n.b                        # number of mtd sampled
  n.cv <- 51                        # number of different cost/vsl ratio values
  base.cv <- 26                     # index for base case cost/base vsl ratio
  high.cv <- 24                     # index for base case cost/high vsl ratio
  low.cv <- 28                      # index for base case cost/low vsl ratio

  n.x <- 51                         # number of bioassay outcomes
  n.reg <- 3                        # number of regulatory control options

  p.pos <- c(0.5, 0.8, 0.5, 0.8)  # probability that potency is non-zero
  LD50 <- c(8000, 8000, 60, 60)   # lethal dose 50 from tier 1
  b.tumor <- 0.02                   # background tumor rate
  alpha <- -log(1-b.tumor)          # background tumor parameter for one-hit model
  mu.Kt <- 0.83                     # mean of ratio of log(TD50) to log(LD50)
  sigma.Kt <- 0.79                  # st dev of ratio of log(TD50) to log(LD50)
  mu.Ks <- -2.3                     # mean of ratio of MTD to LD50
  sigma.Ks <- 1.4                   # st dev of ratio of MTD to LD50
  sigma.s <- 1.2                    # st dev of ln(1/MTD) given beta

  vsl <- c(5,7,12)*10^6             # value of cancer case prevented ($/cancer)
  r <- c(3,5,7)/100                 # discount rate
  low <- 1                          # index for sensitivity - "high" case
  base <- 2                         # index for sensitivity - "base" case
  high <- 3                         # index for sensitivity - "low" case
  pop <- 280*10^6                   # total population exposed(persons/year)
  cost.99 <-10^seq(6,10,4/(n.cv/3-1))   # cost of 99% control option ($/year)

  c.tier2 <- 0.2*10^6               # cost of tier 2 testing (PV $)
  c.tier3 <- 1.3*10^6               # cost of tier 3 testing (PV $)
  t.tier2 <- 1.5                    # time testing & analysis (yrs)
  t.tier3 <- 5                      # time testing & analysis (yrs)

  seed <- 929                       # random seed (integer between 0 and 1023)
  hold <- 929                       # place holder values replaced in "for" loops

  n.ones <- rep(1, n.b)             # column of n ones
  ns.ones <- rep(1, n.s)            # column of n.s ones
  nx.ones <- rep(1, n.x)            # column of n.x ones


# ======================================================
# Set maximum object size to accommodate largest matrix
# ======================================================

  size <- (n.b+1)*(n.s)*(n.x)*8
  options(object.size=size)
```

```
# ========================
# Value of the random seed
# ========================

  set.seed(seed)


# ================================================
# Bioassay results - number of rats with tumors, x
# ================================================

  x <- seq(0, by=1, length=n.x)


# ================================
# Control efficiency, e (percent)
# ================================

  e <- seq(0, by=0.99/(n.reg-1), length=n.reg)


# ================================
# Ratio: cost of regulating to VSL
# ================================

  cv.99 <- sort(cost.99%*%t(1/c(5,7,12)))/10^6
  q <- -log(1-e[n.reg])/cv.99
  cv.ratio <- -log(1-rep(1, n.cv)%*%t(e))/(q%*%t(rep(1, n.reg)))


# ============================================================
# Decision rule for an unconstrained Bayesian decision maker.
# Objective: maximize expected net societal benefit.
# ============================================================

  Max.NB <- function (new, old)
  {
    ifelse(new-old>0, new, old)
  }


# ================================================
# Input values for cases A, B, C, and D
# ================================================

  M.beta.bar <- rep(hold, 4)
  M.beta.pos <- matrix(rep(hold, n.b*4), ncol=4)
  M.mtd <- matrix(rep(hold, n.s*4), ncol=4)
  M.bp.dose <- matrix(rep(hold, 6*4), ncol=4)

for (case in 1:4)
{

# ====================================
# Positive potency, beta (mg/kg/day)^-1
# ====================================

# Distribution of ratio: TD50/LD50
  K <- rnorm(n.b, mu.Kt, sigma.Kt)

# TD50 as a fraction of LD50
  TD50 <- (10^-K)*LD50[case]
```

```
# Convert TD50 into Beta
  beta <- (log(2)-alpha)/TD50
  beta <- sort(beta)


# ======================================
# Maximum tolerated dose, MTD (mg/kg/day)
# ======================================

# Distribution of ratio: MTD/LD50 (data from Gombar et al. 1991)
  K <- rlnorm(n.s, mu.Ks, sigma.Ks)

# MTD as a fraction of LD50
  mtd <- K*LD50[case]
  mtd <- sort(mtd)

# Expected value of potency
  beta.bar <- p.pos[case]*mean(beta)


# ================
# Break Point Dose
# ================

  bp.dose <- (cv.ratio[low.cv,2]-cv.ratio[low.cv,1])*(-70)
  bp.dose <- bp.dose/(e[2]-e[1])/pop
  bp.dose <- bp.dose + exp(-alpha)
  bp.dose <- log(bp.dose) + alpha
  bp.dose <- - bp.dose/beta.bar
  dose <- bp.dose

  bp.dose <- (cv.ratio[base.cv,2]-cv.ratio[base.cv,1])*(-70)
  bp.dose <- bp.dose/(e[2]-e[1])/pop
  bp.dose <- bp.dose + exp(-alpha)
  bp.dose <- log(bp.dose) + alpha
  bp.dose <- - bp.dose/beta.bar
  dose <- c(bp.dose, dose)

  bp.dose <- (cv.ratio[high.cv,2]-cv.ratio[high.cv,1])*(-70)
  bp.dose <- bp.dose/(e[2]-e[1])/pop
  bp.dose <- bp.dose + exp(-alpha)
  bp.dose <- log(bp.dose) + alpha
  bp.dose <- - bp.dose/beta.bar
  dose <- c(bp.dose, dose)

  bp.dose <- (cv.ratio[low.cv,3]-cv.ratio[low.cv,2])*(-70)
  bp.dose <- bp.dose/(e[3]-e[2])/pop
  bp.dose <- bp.dose + exp(-alpha)
  bp.dose <- log(bp.dose) + alpha
  bp.dose <- - bp.dose/beta.bar
  dose <- c(bp.dose, dose)

  bp.dose <- (cv.ratio[base.cv,3]-cv.ratio[base.cv,2])*(-70)
  bp.dose <- bp.dose/(e[3]-e[2])/pop
  bp.dose <- bp.dose + exp(-alpha)
  bp.dose <- log(bp.dose) + alpha
  bp.dose <- - bp.dose/beta.bar
  dose <- c(bp.dose, dose)

  bp.dose <- (cv.ratio[high.cv,3]-cv.ratio[high.cv,2])*(-70)
  bp.dose <- bp.dose/(e[3]-e[2])/pop
  bp.dose <- bp.dose + exp(-alpha)
  bp.dose <- log(bp.dose) + alpha
```

```
  bp.dose <- - bp.dose/beta.bar
  dose <- c(bp.dose, dose)


# ============
# Store Values
# ============

  M.beta.bar[case] <- beta.bar
  M.bp.dose[,case] <- dose
  M.mtd[,case] <- mtd
  M.beta.pos[,case] <- beta

} # end "case" loop

# ========================================
# Exposure weighted average dose (mg/kg/day)
# ========================================

# Range dose from 10^-9 to 10^-1
  z1 <- 10^seq(-9, by=3/15; length=15)
  z2 <- 10^seq(-6, by=4/80, length=80)
  z3 <- 10^seq(-2, by=1/5, length=6)
  dose <- sort(c(M.bp.dose, z1, z2, z3))
  n.d <- count.rows(dose)
  nd.ones <- rep(1, n.d)          # column of n.d ones

  header <- c("Case_A", "Case_B", "Case_C", "Case_D")
  dimnames(M.beta.pos) <- list(NULL, header)
  dimnames(M.mtd) <- list(NULL, header)

  write.table(M.beta.pos, "beta.txt", sep="\t")
  write.table(M.mtd, "mtd.txt", sep="\t")
  write(dose, "dose.txt", ncol=1)


# ================================
# Testing cost and discount factor
# ================================

# Action after tier 2
  df2 <- 1/(1+r[base])^t.tier2
  test.cost.2 <- c.tier2*r[base]

# Action after tier 3
  df3 <- 1/(1+r[base])^(t.tier2+t.tier3)
  test.cost.3 <- c.tier2*r[base] + c.tier3*r[base]*df2


# ============================================
# VOI and Optimal Testing for Cases A, B, and C
# ============================================

  n <- n.b + 1
  M.beta <- matrix(rep(hold, n*4), ncol=4)
  M.prob <- matrix(rep(hold, n*4), ncol=4)
  M.can <- matrix(rep(hold, n.d*4), ncol=4)
  M.EVSI <- matrix(rep(hold, n.d*4), ncol=4)
  M.test <- matrix(rep(hold, n.d*n.cv*3), ncol=n.d)
  M.act.0 <- matrix(rep(hold, n.d*4), ncol=4)
```

```
for (case in 1:3)
{

  n <- n.b
  n.ones <- rep(1, n)
  beta <- M.beta.pos[,case]
  mtd <- M.mtd[,case]


# ================================
# Posterior Probability given MTD
# ================================

  s <- 10^(log10(1/mtd)-0.4)
  mu.s <- log(beta) - sigma.s^2/2

# Brand and Small (1995), equation (20)
# Numerator: likelihood of mtd given prior beta
  p.post.mtd <- dlnorm(n.ones%*%t(s), meanlog=mu.s%*%t(ns.ones), sdlog=sigma.s)
  p.post.mtd <- matrix(p.post.mtd, nrow=n)

# Denominator: sum of likelihood of mtd for all possible beta
  p.post.mtd <- p.post.mtd/(n.ones%*%(t(n.ones)%*%p.post.mtd))

# Back out prior probability of beta implied by posterior given mtd
  p.prior <- p.post.mtd%*%ns.ones/n.s

# Generate unconditional probability of "s"
  p.uncond.s <- ns.ones/n.s


# ==================================
# Adjust values to include zero beta
# ==================================

  beta <- c(0, beta)
  n <- n+1
  n.ones <- rep(1, n)
  p.prior <- c((1-p.pos[case]), p.prior*p.pos[case])
  p.post.mtd <- rbind(t(ns.ones)*(1-p.pos[case]), p.post.mtd*p.pos[case])


# ============================================
# "Added" annual risk of cancer above background
# ============================================

  R <-(-exp(-alpha-beta%*%t(dose))+exp(-alpha))/70
  R.0 <- t(p.prior)%*%R
  R.mtd <- t(p.post.mtd)%*%R

# Initial value for summed object in "i" loop
  NB.bio <- matrix(rep(0, n.d*n.s*n.cv), ncol=n.d)
  nb.bio.x <- matrix(rep(0, n.d*n.s*n.cv), ncol=n.d)


# ===================================
# Posterior Probability given Bioassay
# ===================================

# Probability of tumor in rodents given MTD
  p.tumor <- 1-exp(-alpha-beta%*%t(mtd))
```

```
for (i in 1:n.x) # repeat for each value of test result "x"
{

# Numerator: product of likelihood of "x" given beta|mtd and prob of beta|mtd
  p.post.bio <- dbinom(x[i], 50, p.tumor)
  p.post.bio <- matrix(p.post.bio, nrow=n)*p.post.mtd

# Denominator: sum of the numerator for all possible beta
  p.x.mtd <- t(t(n.ones)%*%p.post.bio)

# Posterior probability of beta given "x"
  p.post.bio <- p.post.bio/(n.ones%*%t(p.x.mtd))


# ============================
# NB from Bioassay Information
# ============================

  R.bio <- t(p.post.bio)%*%R

for (j in 1:n.cv) # repeat for each cv.ratio
{
# ==================
# NB given mtd and x
# ==================

# Initial values of expected net benefit: 0% control
  nb.bio <- matrix(rep(0, n.d*n.s), ncol=n.d)

for (k in 2:n.reg) # NB for each regulatory option above 0%
{

# Net benefit (per capita as a proportion of vsl)
  nb <- R.bio*e[k]*pop - cv.ratio[j,k]
  nb.bio <- Max.NB(nb, nb.bio)

} # end "k" for loop (n.reg)

# ================================
# NB averaged over all possible "x"
# ================================

  z1 <- 1+(j-1)*n.s
  z2 <- j*n.s
  nb.bio.x[z1:z2,] <- nb.bio*(p.x.mtd%*%t(nd.ones))

} # end "j" for loop (n.cv)

  NB.bio <- NB.bio + nb.bio.x

} # end "i" for loop (n.x)


# ============================================
# Initial values for objects in "i" an "j" loops
# ============================================

  mat.hold <- matrix(rep(hold, n.d*n.cv), ncol=n.d)
  NB.0 <- mat.hold          # prior
  NB.t <- mat.hold          # optimal testing

  act.0 <- matrix(rep(0, n.d*n.cv), ncol=n.d)
```

```
for (i in 1:n.cv) # expected NB for each cv.ratio
{

# Initial values of expected net benefit: 0% control
  nb.0 <- t(rep(0, n.d))
  nb.mtd <- matrix(rep(0, n.d*n.s), ncol=n.d)

for (j in 2:n.reg) # NB for each regulatory option above 0%
{
  cost <- cv.ratio[i,j]

# ========================
# NB given only prior info
# ========================

# Net benefit (per capita as a proportion of vsl[base])
  nb <- R.0*e[j]*pop - cost
  act.0[i,] <- ifelse(nb > nb.0, e[j], act.0[i,])
  nb.0 <- Max.NB(nb, nb.0)


# ========================
# NB given only mtd info
# ========================

# Net benefit (per capita as a proportion of vsl[base])
  nb <- R.mtd*e[j]*pop - cost
  nb.mtd <- Max.NB(nb, nb.mtd)

} # end "j" for loop (n.reg)


# ====================
# Expected net benefit
# ====================

# Only prior information
  NB.0[i,] <- nb.0*vsl[base]

# Bioassay
  z1 <- 1+(i-1)*n.s
  z2 <- i*n.s
  nb.bio <- NB.bio[z1:z2,]

# Tiered Testing
  tier2 <- nb.mtd*vsl[base]*df2 - test.cost.2
  tier3 <- nb.bio*vsl[base]*df3 - test.cost.3
  MaxNB <- Max.NB(tier2, tier3)
  NB.t[i,] <- t(p.uncond.s)%*%MaxNB

} # end "i" for loop (n.cv)


# ========================
# Optimal Testing Decision
# ========================

  test.t1 <- ifelse(NB.t > NB.0, 1, act.0)
```

```
# ============
# Store Values
# ============

  z1 <- (case-1)*n.cv + 1
  z2 <- case*n.cv

  M.test[z1:z2,] <- test.t1
  M.beta[,case] <- beta
  M.prob[,case] <- p.prior
  M.can[,case] <- pop*R.0
  M.EVSI[,case] <- NB.t[base.cv,] - NB.0[base.cv,]
  M.act.0[,case] <- act.0[base.cv,]

} # end "case" loop

  z1 <- 1
  z2 <- n.cv
  test.A <- M.test[z1:z2,]

  z1 <- 1+z2
  z2 <- z2+n.cv
  test.B <- M.test[z1:z2,]

  z1 <- 1+z2
  z2 <- z2+n.cv
  test.C <- M.test[z1:z2,]


# ==============================
# VOI and sensitivity for Case D
# ==============================

  n <- n.b
  n.ones <- rep(1, n)
  beta <- M.beta.pos[,4]
  mtd <- M.mtd[,4]

# ==============================
# Posterior Probability given MTD
# ==============================

  s <- 10^(log10(1/mtd)-0.4)
  mu.s <- log(beta) - sigma.s^2/2
  p.post.mtd <- dlnorm(n.ones%*%t(s), meanlog=mu.s%*%t(ns.ones), sdlog=sigma.s)
  p.post.mtd <- matrix(p.post.mtd, nrow=n)
  p.post.mtd <- p.post.mtd/(n.ones%*%(t(n.ones)%*%p.post.mtd))
  p.prior <- p.post.mtd%*%ns.ones/n.s
  p.uncond.s <- ns.ones/n.s

# ================================
# Adjust values to include zero beta
# ================================

  beta <- c(0, beta)
  n <- n+1
  n.ones <- rep(1, n)
  p.prior <- c((1-p.pos[4]), p.prior*p.pos[4])
  p.post.mtd <- rbind(t(ns.ones)*(1-p.pos[4]), p.post.mtd*p.pos[4])
```

```
# ============================================================
# "Added" annual risk of cancer above background from exposure
# ============================================================

  R <-(-exp(-alpha-beta%*%t(dose))+exp(-alpha))/70
  R.0 <- t(p.prior)%*%R
  R.mtd <- t(p.post.mtd)%*%R

# ====================
# Objects in "i" loop
# ====================

  NB.bio.x <- matrix(rep(hold, n.d*n.cv*n.s), ncol=n.d)
  NB.bio <- matrix(rep(0, n.d*n.s*n.cv), ncol=n.d)
  cancer.bio <- matrix(rep(0, n.d*n.s), ncol=n.d)
  cost.bio <- matrix(rep(0, n.d*n.s), ncol=n.d)

# ====================================
# Posterior Probability given Bioassay
# ====================================

  p.tumor <- 1-exp(-alpha-beta%*%t(mtd))

for (i in 1:n.x) # repeat for each value of test result "x"
{
  p.post.bio <- dbinom(x[i], 50, p.tumor)
  p.post.bio <- matrix(p.post.bio, nrow=n)*p.post.mtd
  p.x.mtd <- t(t(n.ones)%*%p.post.bio)
  p.post.bio <- p.post.bio/(n.ones%*%t(p.x.mtd))
  R.bio <- t(p.post.bio)%*%R

for (j in 1:n.cv) # repeat for each cv.ratio
{
# ==================
# NB given mtd and x
# ==================

  nb.bio <- matrix(rep(0, n.d*n.s), ncol=n.d)

for (k in 2:n.reg) # NB for each regulatory option above 0%
{

  nb <- R.bio*e[k]*pop - cv.ratio[j,k]
  nb.bio <- Max.NB(nb, nb.bio)

} # end "k" for loop (n.reg)

# ================================
# NB averaged over all possible "x"
# ================================

  z1 <- 1+(j-1)*n.s
  z2 <- j*n.s
  NB.bio.x[z1:z2,] <- nb.bio*(p.x.mtd%*%t(nd.ones))

} # end "j" for loop (n.cv)

  NB.bio <- NB.bio + NB.bio.x
```

```
# ================================================================
# Cancers prevented and costs saved given bioassay (base case cost)
# ================================================================

  nb.bio <- matrix(rep(0, n.d*n.s), ncol=n.d)
  cancer.bio.x <- matrix(rep(0, n.d*n.s), ncol=n.d)
  cost.bio.x <- matrix(rep(0, n.d*n.s), ncol=n.d)

for (h in 2:n.reg)
{
  cancer <- R.bio*e[h]*pop
  cost <- cv.ratio[base.cv, h]
  nb <- cancer - cost
  cancer.bio.x <- ifelse(nb > nb.bio, cancer, cancer.bio.x)
  cost.bio.x <- ifelse(nb > nb.bio, cost, cost.bio.x)
  nb.bio <- Max.NB(nb, nb.bio)

} # end "h" for loop (n.reg)

  cancer.bio <- cancer.bio + cancer.bio.x*(p.x.mtd%*%t(nd.ones))
  cost.bio <- cost.bio + cost.bio.x*(p.x.mtd%*%t(nd.ones))

} # end "i" for loop (n.x)

# ============================================
# Initial values for objects in "i" an "j" loops
# ============================================

  mat.hold <- matrix(rep(hold, n.d*n.cv), ncol=n.d)
  NB.perfect <- mat.hold   # perfect
  NB.0 <- mat.hold         # prior
  NB.b <- mat.hold         # optimal testing - base case
  NB.vh <- mat.hold        # optimal testing - high vsl
  NB.vl <- mat.hold        # optimal testing - low vsl
  NB.dh <- mat.hold        # optimal testing - high discount rate
  NB.dl <- mat.hold        # optimal testing - low discount rate

  act.0 <- matrix(rep(0, n.d*n.cv), ncol=n.d)

for (i in 1:n.cv) # expected NB for each cv.ratio
{
  nb.0 <- t(rep(0, n.d))
  nb.mtd <- matrix(rep(0, n.d*n.s), ncol=n.d)
  nb.perfect <- matrix(rep(0, n.d*n), ncol=n.d)

# ========================================
# NB from Prior, MTD, and Perfect Information
# ========================================

for (j in 2:n.reg) # NB for each regulatory option above 0%
{
  cost <- cv.ratio[i,j]

# ======================
# NB given only prior info
# ======================

  nb <- R.0*e[j]*pop - cost
  act.0[i,] <- ifelse(nb > nb.0, e[j], act.0[i,])
  nb.0 <- Max.NB(nb, nb.0)
```

```
# ======================
# NB given only mtd info
# ======================

  nb <- R.mtd*e[j]*pop - cost
  nb.mtd <- Max.NB(nb, nb.mtd)

# ====================
# NB given perfect info
# ====================

  nb <- R*e[j]*pop - cost
  nb.perfect <- Max.NB(nb, nb.perfect)

} # end "j" for loop (n.reg)


# ====================
# Expected net benefit
# ====================

  NB.0[i,] <- nb.0
  NB.perfect[i,] <- t(p.prior)%*%nb.perfect

# ============================
# NB from optimal tiered testing
# ============================

  z1 <- 1+(i-1)*n.s
  z2 <- i*n.s
  nb.bio <- NB.bio[z1:z2,]

# Base case
  df2 <- 1/(1+r[base])^t.tier2
  test.cost.2 <- c.tier2*r[base]
  df3 <- 1/(1+r[base])^(t.tier2+t.tier3)
  test.cost.3 <- c.tier2*r[base] + c.tier3*r[base]*df2

  tier2 <- nb.mtd*vsl[base]*df2 - test.cost.2
  tier3 <- nb.bio*vsl[base]*df3 - test.cost.3
  MaxNB <- Max.NB(tier2, tier3)
  NB.b[i,] <- t(p.uncond.s)%*%MaxNB

# Sensitivity: Low VSL
  tier2 <- nb.mtd*vsl[low]*df2 - test.cost.2
  tier3 <- nb.bio*vsl[low]*df3 - test.cost.3
  MaxNB <- Max.NB(tier2, tier3)
  NB.vl[i,] <- t(p.uncond.s)%*%MaxNB

# Sensitivity: High VSL
  tier2 <- nb.mtd*vsl[high]*df2 - test.cost.2
  tier3 <- nb.bio*vsl[high]*df3 - test.cost.3
  MaxNB <- Max.NB(tier2, tier3)
  NB.vh[i,] <- t(p.uncond.s)%*%MaxNB

# Sensitivity: Discount Rate High
  df2 <- 1/(1+r[high])^t.tier2
  test.cost.2 <- c.tier2*r[high]
  df3 <- 1/(1+r[high])^(t.tier2+t.tier3)
  test.cost.3 <- c.tier2*r[high] + c.tier3*r[high]*df2

  tier2 <- nb.mtd*vsl[base]*df2 - test.cost.2
  tier3 <- nb.bio*vsl[base]*df3 - test.cost.3
```

```
  MaxNB <- Max.NB(tier2, tier3)
  NB.dh[i,] <- t(p.uncond.s)%*%MaxNB

# Sensitivity: Discount Rate Low
  df2 <- 1/(1+r[low])^t.tier2
  test.cost.2 <- c.tier2*r[low]
  df3 <- 1/(1+r[low])^(t.tier2+t.tier3)
  test.cost.3 <- c.tier2*r[low] + c.tier3*r[low]*df2

  tier2 <- nb.mtd*vsl[base]*df2 - test.cost.2
  tier3 <- nb.bio*vsl[base]*df3 - test.cost.3
  MaxNB <- Max.NB(tier2, tier3)
  NB.dl[i,] <- t(p.uncond.s)%*%MaxNB

} # end "i" for loop (n.cv)


# ============================================================
# Value of Information and optimal testing decision after Tier 1
# ============================================================

# Base case
  df2 <- 1/(1+r[base])^t.tier2
  test.cost.2 <- c.tier2*r[base]
  df3 <- 1/(1+r[base])^(t.tier2+t.tier3)
  test.cost.3 <- c.tier2*r[base] + c.tier3*r[base]*df2

  EV.0 <- NB.0[base.cv,]*vsl[base]
  EV.tiered <- NB.b[base.cv,]
  EV.perfect <- NB.perfect[base.cv,]*vsl[base]

  EVPI <- EV.perfect - EV.0
  EVSI <- EV.tiered - EV.0

  tier1 <- NB.0*vsl[base]
  test.t1 <- ifelse(NB.b > tier1, 1, act.0)

# Sensitivity: Discount Rate (high)
  test.dh <- ifelse(NB.dh > tier1, 1, act.0)
  EVSI.dh <- NB.dh - tier1

# Sensitivity: Discount Rate (low)
  test.dl <- ifelse(NB.dl > tier1, 1, act.0)
  EVSI.dl <- NB.dl - tier1

# Sensitivity: VSL (high)
  tier1 <- NB.0*vsl[high]
  test.vh <- ifelse(NB.vh > tier1, 1, act.0)
  EVSI.vh <- NB.vh - tier1

# Sensitivity: VSL (low)
  tier1 <- NB.0*vsl[low]
  test.vl <- ifelse(NB.vl > tier1, 1, act.0)
  EVSI.vl <- NB.vl - tier1
```

```
# ============================================================
# Expected cancers prevented and costs saved (base case cost)
# ============================================================

# Initial values: 0% control
  cancer.0 <- rep(0, n.d)
  cost.0 <- rep(0, n.d)
  nb.0 <- rep(0, n.d)

  cancer.mtd <- matrix(rep(0, n.d*n.s), ncol=n.d)
  cost.mtd <- matrix(rep(0, n.d*n.s), ncol=n.d)
  nb.mtd <- matrix(rep(0, n.d*n.s), ncol=n.d)

for (i in 2:n.reg) # NB for each regulatory option above 0%
{
  cost <- cv.ratio[base.cv, i]

  cancer <- R.0*e[i]*pop
  nb <- cancer - cost
  cancer.0 <- ifelse(nb > nb.0, cancer, cancer.0)
  cost.0 <- ifelse(nb > nb.0, cost, cost.0)
  nb.0 <- Max.NB(nb, nb.0)

  cancer <- R.mtd*e[i]*pop
  nb <- cancer - cost
  cancer.mtd <- ifelse(nb > nb.mtd, cancer, cancer.mtd)
  cost.mtd <- ifelse(nb > nb.mtd, cost, cost.mtd)
  nb.mtd <- Max.NB(nb, nb.mtd)

} # end "i" for loop (n.reg)

  z1 <- 1+(base.cv-1)*n.s
  z2 <- base.cv*n.s
  tier2 <- nb.mtd*vsl[base]*df2 - test.cost.2
  tier3 <- NB.bio[z1:z2,]*vsl[base]*df3 - test.cost.3

  cancer.test <- t(p.uncond.s)%*%ifelse(tier3 > tier2, cancer.bio*df3,
     cancer.mtd*df2)
  cost.test <- t(p.uncond.s)%*%ifelse(tier3 > tier2, cost.bio*df3,
     cost.mtd*df2)
  test.mtd <- ifelse(tier3 > tier2, 1, 0)

  EV.cancer <- (cancer.test - cancer.0)
  EV.cost <- (cost.0 - cost.test)*vsl[base]


# ============
# Store Values
# ============

  test.D <- test.t1
  M.beta[,4] <- beta
  M.prob[,4] <- p.prior
  M.can[,4] <- R.0*pop
  M.EVSI[,4] <- EVSI
  M.act.0[,4] <- act.0[base.cv,]
```

Chapter 4: The Value of Tiered Testing to a Constrained Decision Maker

1. Introduction

The previous chapter explored how carcinogenicity data collected through the VCCEP may be used to inform risk management decisions, and it derived the optimal stopping criteria for a chemical where Tier 1 screening data have been collected, from the perspective of a net benefits maximizing decision maker. We assumed that the decision maker is able to regulate based on lower tier tests without a bioassay result. However, for chemicals already in use, the current regulatory structure does not ordinarily allow for regulation of a chemical as a carcinogen without either bioassay results or human epidemiological results. To the extent that a decision maker is constrained by the necessity of a bioassay test result to regulate, the value of testing will tend to increase since an increase in net benefits can only be derived after testing. In addition, decision makers are often constrained by statutory requirements such that maximizing net benefit is not the sole (or even primary) criterion for taking regulatory action.

In this chapter we examine the differences in optimal testing decisions between a net benefit maximizing decision maker and a constrained decision maker, defined as one who cannot regulate by analogy (i.e., without "hard" data). The analysis quantifies the estimated loss in societal welfare from restricting regulators to act only after bioassay data on a specific chemical is available. In addition, it will quantify the differences in net benefits as well as cancers prevented and control costs for three decision criteria: maximizing societal net benefits, ensuring maximum exposure control while net benefits are positive, and controlling to the maximum extent technologically feasible while the lifetime risk of cancer exceeds 10^{-6}.

2. Methods

2.1 Decision Model

All previous value of information analyses on toxicological testing assumed the "traditional" expected net benefit maximizing decision maker (NBMDM),[1-4] and this is the common perspective taken in most applications as discussed in Chapter 2. The NBMDM regulates a chemical based on a subjective prior assessment of potency updated by indirect measures in addition to "hard" data from animal bioassay, and chooses a level of regulation that will maximize net societal benefit. In practice, either bioassay results or human epidemiological results are necessary for making regulatory decisions for suspected carcinogens. Figure 4.1 represents a simplified schematic of the decision to require the next level of testing for an unconstrained NBMDM and a constrained decision maker (CDM). For the CDM, each level of testing refines the estimate of potency, but no control actions can be taken based on presumed carcinogenicity until a bioassay result is in hand (i.e., assuming that insufficient epidemiological data are available). Therefore, each decision to stop testing yields no costs or benefits other than testing costs already incurred.

In this analysis, we compare optimal testing strategies for three different types of CDMs to the Unconstrained NBMDM. All three must first have Tier 3 test results before they are allowed to take regulatory action, but differ in their decision criterion given the constraint. Like the unconstrained NBMDM, the first CDM (CDM-Max) chooses the control option that maximizes the annualized net benefit for each control option k:

$$NB_k = \frac{\varepsilon_k v R n - c_k}{(1+r)^t} \qquad (1)$$

where

- ε_k is the control efficiency for regulatory strategy k (proportion),
- v is the value of a case of cancer prevented (2000 U.S. dollars),
- R is the average annual risk of cancer to population (probability),
- n is the population exposed (persons/year),
- c_k is the annualized cost of regulatory control (2000 U.S. dollars/year).
- r is the discount rate (percentage), and
- t is the delay in action from testing (years).

The expected net benefit from testing is the difference between the expected net benefit from the optimal control option given test information and the annualized cost of testing. For CDM-Max, since no action can be taken without bioassay test result, the prior action is always zero, and therefore net benefits are always zero. Therefore, for CDM-Max, the net benefit of testing represents the net value of information. This decision maker will conduct Tier 2 tests as long as the net value of information is positive.

The second CDM (CDM-Pos) chooses the maximum control level available that will still yield positive net benefits (i.e., ensure that benefits justify costs). If only two control options are available (no control vs. control), the optimal action for this decision maker is identical to that of the NBMDM. However, as more control options become available, the greater the deviation in the optimal action. CDM-Pos, like CDM-Max, will test Tier 2 if the expected net value of information is positive.

The third CDM (CDM-Risk) regulates based only on estimates of risk. In general, an acceptable level of elevation in lifetime cancer risk in the regulatory context is considered to be one in a million, though different levels have been used in regulatory

decision making.[5] Here we assume that this decision maker will control exposures to the maximum extent technologically feasible, until expected lifetime risk at or below 10^{-6}. We further assume that after Tier 1 CDM-Risk will test Tier 2 if the 99th percentile value of the distribution of lifetime risk implied by Tier 1 test results exceeds 10^{-6}.

In this analysis, we use the same assumptions about modeling the control decisions and costs as we used in Chapter 3 with one important difference. In the base case analysis, instead of using three levels of control as we used in chapter 3, here we examined the case where ten levels of control are available: 0%, 11%, 22%, 33%, 44%, 55%, 66%, 77%, 88%, and 99%. We decided to use more levels of control to better illustrate the differences in the net benefits and optimal testing decision for the different CDMs. We have not evaluated in either chapter the option of completely banning the use of a chemical (i.e., 100% control).

2.2 Risk Model

We model the lifetime risk of developing cancer the same as in Chapter 3 using a one-hit model that assumes the risk of tumor is equal to the risk of developing cancer at an unspecified site:

$$1-\exp\left(-\alpha-\beta\bar{d}\right) \tag{2}$$

where

- $1-\exp(-\alpha)$ represents the background tumor rate,
- β is the carcinogenic potency $(\text{mg/kg/day})^{-1}$, and
- exposure weighted average dose $\bar{d}$ (mg/kg/day).

The annual risk of cancer above the background level, R, is estimated by dividing the lifetime risk above the background rate by 70 years/lifetime, the approximate human life expectancy:

$$R = \frac{\exp(-\alpha)\left[1-\exp(-\beta d)\right]}{70} \tag{3}$$

In this analysis we assume the uncertainty faced by the decision maker relates to the true value of carcinogenic potency, β, and the potential results of testing. All other input values are assumed to be known with certainty. The uncertain input values were generated using the random sampling function in S-Plus 2000. Table 3.2 in the previous chapter summarizes the parameters for distributions the distributions used to characterize uncertainty. Using the same methods outlined in the previous chapter, we model the prior probability of potency as a sum of a probability mass at zero potency (i.e., not a carcinogen) and a continuous parametric distribution for positive potency based on Tier 1 test results for LD50 and mutagenicity. Based on the Tier 1 information, we predict the likely Tier 2 test results using simulation and consider all possible bioassay outcomes to calculate the posterior distributions for potency for each information scenario (See previous chapter for details).

2.3 Illustrative Case

For this chapter we use the hypothetical case D from the previous chapter, which assumes that the chemical of interest tests positive in the mutagenicity test and has a relatively high acute toxicity (LD50 of 60 mg/kg), to illustrate the approach. Test results for this case imply an upper bound value of expected potency since an LD50 of 60 mg/kg correspond to the 5th percentile of LD50 values reported in Gombar et al.[6] Since it

represents an upper bound of potential Tier 1 results, the results will represent an upper bound for the risk of cancer given a level of exposure and the benefits from control.

Table 4.1 summarizes the base case values of constant inputs and the range of values used in the sensitivity analysis. For all cases, we evaluate the VOI for exposure weighted average doses ranging from 10^{-9} to 10^{-3} mg/kg/day. This range corresponds to the range of average U.S. population exposures for approximately 18 of the 20 rodent carcinogens from Table 3.3 of the previous chapter.[7] The value of information is calculated using the procedures explained in the previous chapter for a range of values of exposure weighted average dose ($\bar{d}$), regulatory options, costs of control, and dollar value of a cancer case avoided (See appendix for the complete S-Plus code).

3. Results

3.1 Base Case Analysis

Figure 4.2(a) plots the optimal regulatory action for the unconstrained NBMDM given only Tier 1 information for the base case assumptions that the cost function is quadratic, the cost of 99% control is $100 million per year, the value of a cancer case avoided is $7 million, and the discount rate is 5%. The plot shows that given Tier 1 test results of positive mutagenicity and high acute toxicity (defined as an LD50 of at least 60 mg/kg), the optimal prior action is to not control for exposure weighted doses below 2.6×10^{-6} mg/kg/day and 99% control becomes optimal at 5.5×10^{-5} mg/kg/day.

Figure 4.2 (b) plots the expected value of information for the unconstrained NBMDM from testing Tier 2 net of testing and delay costs for the base case. The cost of delay is the opportunity cost of delaying action while tests are conducted and results

analyzed. Here, the greater the discount rate, the greater the opportunity cost. The plot shows that the discounted annual expected net benefits peaks at the exposure weighted dose of $7.3x10^{-6}$ mg/kg/day and a value of $11 million per year, where the optimal prior action is to control at 88%. The value of testing is positive between $1.7x10^{-7}$ mg/kg/day, where the optimal prior action is no control, and $3.2x10^{-5}$ mg/kg/day, where the optimal prior action is to control at 88%. So the optimal testing decision given Tier 1 information is no control when the exposure weighted dose is below $1.7x10^{-7}$ mg/kg/day, test Tier 2 if it is between $1.7x10^{-7}$ mg/kg/day and $3.2x10^{-5}$ mg/kg/day, control at 88% if it is between $3.2x10^{-5}$ mg/kg/day and $5.5x10^{-5}$ mg/kg/day, and control at 99% if it is above $5.5x10^{-5}$ mg/kg/day.

Figure 4.2 (c) shows the optimal testing strategy for the unconstrained NBMDM given Tier 1 information varying the cost of 99% control from $1 million per year to $10 billion per year. For a high cost of control and low exposure weighted dose, the optimal action is to not do anything. For low cost of control and high exposure weighted dose, the optimal action is to control at 88% or 99%, without gathering any addition testing information. Although collecting additional toxicological information may help the NBMDM make a better control decision, the cost of delaying action combined with the testing cost is sufficiently high that for these combinations of control cost and exposure, collecting additional information is not optimal. In most cases, the cost of control plays a key role in determining whether Tier 2 testing is optimal.

Figure 4.3 compares the optimal testing strategy given Tier 1 for the unconstrained NBMDM and the three different CDMs for the base case varying the cost of 99% control from $1 million per year to $10 billion per year. The frontier for the

decision of no control versus test Tier 2 is nearly identical for (a) the unconstrained NBMDM, (b) the CDM who maximizes net benefits (CDM-Max), and (c) the CDM who ensures that benefits justify costs (CDM-Pos). However, CDM-Risk, who regulates based only on expected risk, is insensitive to control cost and therefore tests Tier 2 when the dose indicates that the 99th percentile of risk based on Tier 1 results exceeds 10^{-6} lifetime risk of cancer. Thus, CDM-Risk, a "Risk-only" decision maker (in the context of Thompson and Graham[8]) does not take advantage of opportunities to reduce risks when control costs are low, but the lifetime risk of cancer is lower than 10^{-6}. Since none of the CDMs are able to regulate without Tier 3 information, Tier 2 testing is optimal for all exposure weighted dose to the right of the frontier.

Figure 4.4 (a) plots the foregone expected net benefits for the base case from the constraint requiring Tier 3 information for regulatory action. The difference in net benefits between the unconstrained NBMDM and the CDMs grows somewhat proportionally with exposure weighted dose (note that the x axis is on a log scale, while the y axis is linear), such that differences in net benefits range from $0 to nearly $2 billion per year. The monotonic increase in the difference with increase in dose is due to the increase in opportunity cost of waiting to act; though the optimal action is to control without testing, all three CDMs must delay action by 6.5 years for both the Tier 2 and Tier 3 tests results to be collected and analyzed before taking regulatory action. Since the Case D represents an upper bound of Tier 1 test results, an exposure weighted dose of 10^{-3} mg/kg/day implies a little over 1000 expected annual cases of cancer, so the net benefits from controlling at 99% are $7.2 billion. However, discounting the net benefits after 6.5 years at 5% yields discounted net benefits of $5.2 billion, for a difference of nearly $2

billion in net benefits lost per year. Figure 4.4 (b) compares the foregone expected net benefits between the three CDMs. For low doses where the optimal action is to not control for all CDMs, and high doses where the optimal action is to control at 99% for all CDMs, the difference is minimal. However, the difference grows to a maximum of nearly $17 million per year for the CDM-Risk and $7 million per year for the CDM-Pos who ensures positive net benefits.

Figure 4.5(a) plots the difference in expected cancers prevented for the NBMDM and the three CDMs discounted to account for timing. The plot shows that the proportional decreases in cancer cases saved drive the results in Figure 4.4(a) and range from close to 0 to more than 250 cases of cancers, and the differences between CDMs are difficult to see. Figure 4.5(b) compares the difference in expected number of cancers prevented between the CDMs. Here the y-axis ranges in value from 0 to 1.5 cases of cancers. It shows that between, 1.7×10^{-7} mg/kg/day and 3.4×10^{-6} mg/kg/day, the CDM-Risk acts in a way that yields less cancer cases prevented than the CDM-Max. On the other hand, CDM-Pos almost always prevents more cancer cases than the CDM-Max.

Figure 4.6(a) plots the difference in discounted expected control costs incurred for the NBMDM compared to the three CDMs. CDM-Pos and CDM-Risk have higher control costs for a range of doses since higher levels of control would be required under these two decision criteria. However, the costs drop when the optimal action for the unconstrained NBMDM is to control now, while the costs for the CDMs are always incurred 6.5 years in the future after all of the testing and analysis have been completed. Control costs are lowest for CDM-Max compared to CDM-Pos and CDM-Risk in almost all cases since these control costs are always incurred 6.5 years in the future.

3.2 Sensitivity Analysis

Table 4.2 reports the sensitivity of the estimated expected net benefits to changes in value of cancer prevented and discount rate for four levels of exposure weighted dose: 10^{-6}, 10^{-5}, 10^{-4}, and 10^{-3} mg/kg/day. Table 4.3 reports the sensitivity of the break point dose for the decision not to control versus test Tier 2 for all decision makers, and for the decision to test Tier 2 versus control now (at either 88% or 99%) for the unconstrained NBMDM to changes in value of cancer prevented and discount rate assuming a cost of 99% control of $100 million per year.

Increasing the value placed on preventing cancer should increases the net benefits from testing since the benefits of testing and subsequent control action in preventing cancers would increase in value. As table 4.2 shows, increasing the value from $7 million to $12 million increases net benefit of testing for all decision makers and all exposure levels except for a small decrease for CDM-Risk at 10^{-6} mg/kg/day (note that the table present expected net benefits of testing, not the expected value of information). Similarly, decreasing the value from $7 million to $5 million decreases the net benefits of testing.

Since the expected net benefit of testing is the value of information for the CDMs, decreasing the value of cancer prevented from $7 million to $5 million should make testing optimal for a larger range of exposure levels for the CDM-Max and CDM-Pos. As Table 4.3 shows, the increase shifts the break point dose for no control versus testing slightly to the right, while increasing the value to $12 million shifts the frontiers slightly to the left. By definition, the testing strategy of CDM-Risk is not affected by changes in the value of cancer prevented. For the unconstrained NBMDM, the impact of the change

on optimal strategy is ambiguous since an increase in the value will increase the net benefits from testing as well as taking action now. As Table 4.3 shows, in this analysis increasing the value shifts both break point dose values to the left, and decreasing the value shifts both the break point dose values to the right. For the lower range of exposure levels, the impact of the change is driven by the increase in value of testing since the optimal action without testing is no control, which yields zero benefits. On the other hand, at the higher range of exposure, the cost of waiting to act greatly increases with increases in the value of cancer prevented such that controlling now becomes more valuable.

The discount rate affects the annualized cost of testing as well as the cost of waiting to take action. Decreasing the discount rate decreases the annualized cost and the foregone net benefits from waiting such that the value of testing tier 2 should become larger, and testing will be the optimal action for a larger range of exposure levels. As Table 4.2 shows, decreasing the discount rate increases the net benefits of testing for all decision makers and all exposure levels (except for a small decrease for CDM-Risk at 10^{-6} mg.kg/day). Likewise, increasing the discount rate decreases net benefits.

As Table 4.3 shows, decreasing the discount rate from 5% to 3% has only a small impact on the break point dose for the decision not to control versus testing Tier 2, with a slight shift to the left for CDM-Pos. Meanwhile, changing the discount rate from 5% to 7% shifts the break points to the right (except for CDM-Risk). Changing the discount rate from 5% to 3% creates a noticeable shift to the right in the break point dose for testing Tier 2 versus control now for the unconstrained NBMDM. Likewise, changing the rate from 5% to 7% creates a shift to the left in the break point dose.

5. Discussion

The analysis shows that sub-optimal testing using various decision criteria for the most part lead to a net gain to society compared to doing nothing (i.e., no testing and no control), even for the risk only criteria. However, for some ranges of dose and costs, the expected net benefit from a societal perspective of using the approach taken by CDM-Risk (a "Risk only" approach) is negative. In addition, such a criterion misses out on cost-effective interventions to reduce risks below the threshold.[8] On the other hand, ensuring that net benefits are positive (CDM-Pos), or better yet maximized (CDM-Max), allows for these cost-effective investments. Though the net benefits may be positive, there are large differences in net benefits between these three criteria for the "middle" range of exposure levels where the optimal actions differ.

Though we are not worse off in the sense that societal net benefits are not negative, we are not doing as well as we could be by restricting a regulator's ability to control without bioassay information. The restriction is most burdensome when the level of exposure is high since the loss to society between the constrained and unconstrained decision makers grows proportionally with exposure weighted dose. For some classes of chemicals (e.g., pesticides and pharmaceuticals), the burden of proof is on manufacturers to show safety before it is released for general use. For potentially highly toxic and high exposure chemicals, this analysis shows that this approach makes sense.

References

1. L. B. Lave and G. S. Omenn, "Cost-Effectiveness of Short-Term Tests for Carcinogenicity," *Nature*, 324(6092), 29-34 (1986).

2. L. B. Lave and G. S. Omenn, "Screening Toxic-Chemicals - How Accurate Must Tests Be," *Journal of the American College of Toxicology*, 7(5), 565-574 (1988).

3. L. B. Lave, F. K. Ennever, H. S. Rosenkranz et al., "Information Value of the Rodent Bioassay," *Nature*, 336(6200), 631-633 (1988).

4. A. C. Taylor, J. S. Evans, and T. E. McKone, "The Value of Animal Test Information in Environmental-Control Decisions," *Risk Analysis*, 13(4), 403-412 (1993).

5. Stephen G. Breyer, *Breaking the vicious circle : Toward effective risk regulation* (Harvard University Press, Cambridge, MA, 1993).

6. V. K. Gombar, K. Enslein, J. B. Hart et al., "Estimation of Maximum Tolerated Dose for Long-Term Bioassays from Acute Lethal Dose and Structure by Qsar," *Risk Analysis*, 11(3), 509-517 (1991).

7. L. S. Gold, T. H. Slone, and B. N. Ames, "What do animal cancer tests tell us about human cancer risk? Overview of analyses of the carcinogenic potency database," *Drug Metabolism Reviews*, 30(2), 359-404 (1998).

8. K. M. Thompson and J. D. Graham, "Going beyond the single number: Using probabilistic risk assessment to improve risk management," *Human and Ecological Risk Assessment*, 2(4), 1008-1034 (1996).

9. W. Kip Viscusi and JE Aldy, "The Value of a Statistical Life: A Critical Review of Market Estimates throughout the World", Discussion Paper No. 392, (2002). Available at: http://www.law.harvard.edu/programs/olin_center/papers/392_viscusi.htm

10. Robert W. Hahn, "Regulatory Reform: What Do the Government's Numbers Tell Us?," in *Risk, Costs, and Lives Saved: Getting Better Results from Regulation*, edited by Robert W. Hahn (Oxford University Press, The AEI Press, Washington, DC, 1996).

11. Office of Management and Budget, "Economic Analysis of Federal Regulations Under Executive Order 12866", (1996). Available at: http://www.whitehouse.gov/omb/inforeg/riaguide.html

12. M. C. Weinstein, J. E. Siegel, M. R. Gold et al., "Recommendations of the panel on cost-effectiveness in health and medicine," *Jama-Journal of the American Medical Association*, 276(15), 1253-1258 (1996).

13. U.S. Environmental Protection Agency, "Supporting Statement for a Request for OMB Review under the Paperwork Reduction Act", OPPT-2002-0005-0002, (2002).

Tables and Figures

Figure 4.1: Simplified schematic of the testing decision

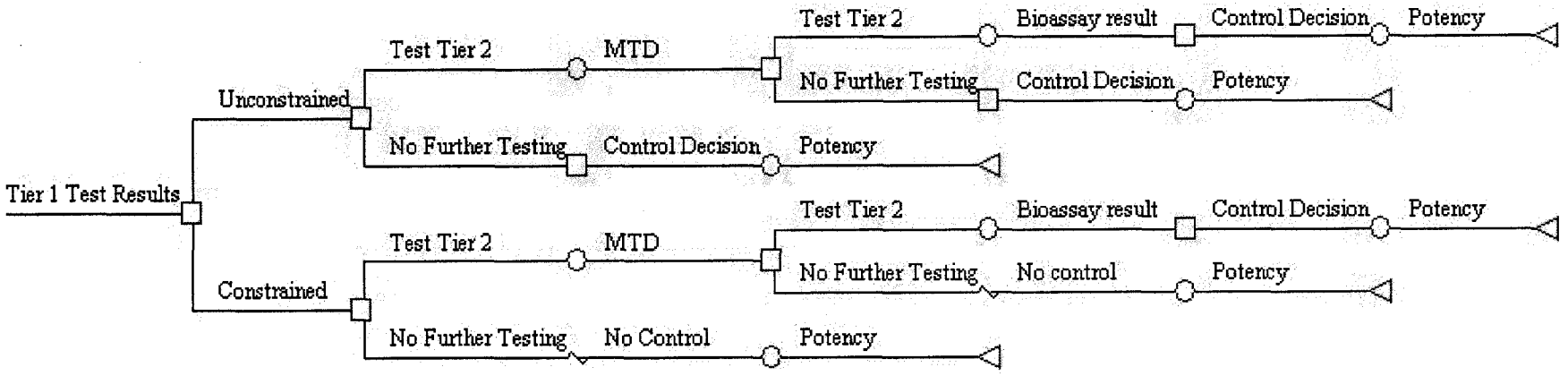

Table 4.1: Constant input values

Input	Symbol	Base Case	Sensitivity	Units	Source
Exposure weighted average population dose	d	10^{-9} to 10^{-3}		mg/kg/day	Gold et al. [7]
Value of cancer prevented	v	\$7 million	\$5 million, \$12 million	2000 dollars per statistical life	Viscusi and Aldy[9]
Efficiency of control k	e_k	0%, 11%, 22%, ..., 99%		percentage	Hypothetical
Cost of 99% control	$c_{99\%}$	\$100 million	\$1 million to \$10 billion	2000 dollar per year	Hypothetical
Discount rate	r	5%	3%, 7%	percentage	Hahn[10], OMB[11], Weinstein et al.[12]
Cost of tier 2 testing	c_{tier2}	\$200,000r		2000 dollars per year	U.S. EPA[13]
Delay in action from tier 2 testing	t_{tier2}	1.5		years	U.S. EPA[13]
Cost of tier 3 testing	c_{tier3}	\$1,300,000r		2000 dollars per year	U.S. EPA[13]
Delay in action from tier 3 testing	t_{tier3}	5		years	U.S. EPA[13]

Figure 4.2: Unconstrained Net Benefits Maximizing Decision Maker (NBMDM)

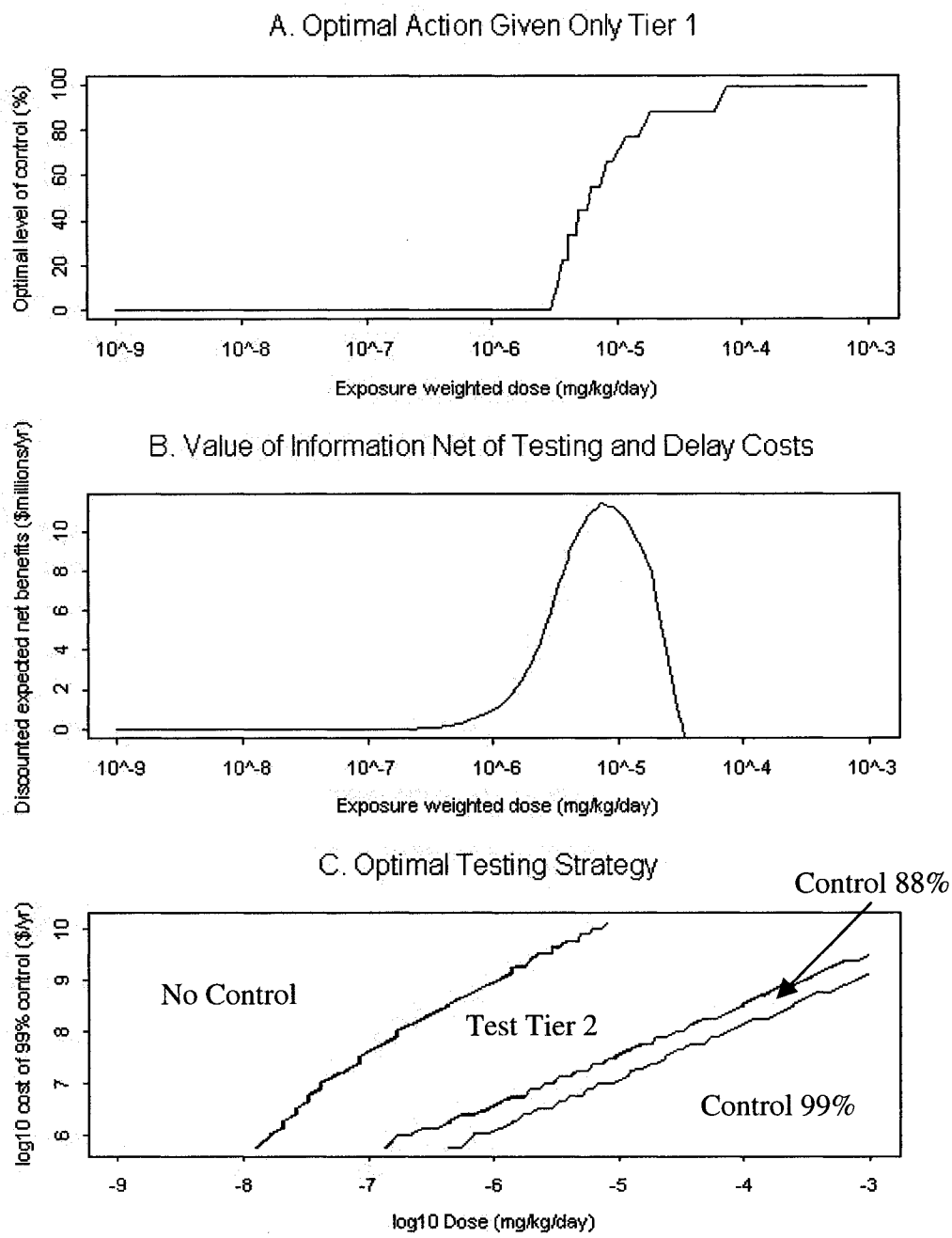

Figure 4.3: Optimal testing strategy given tier 1

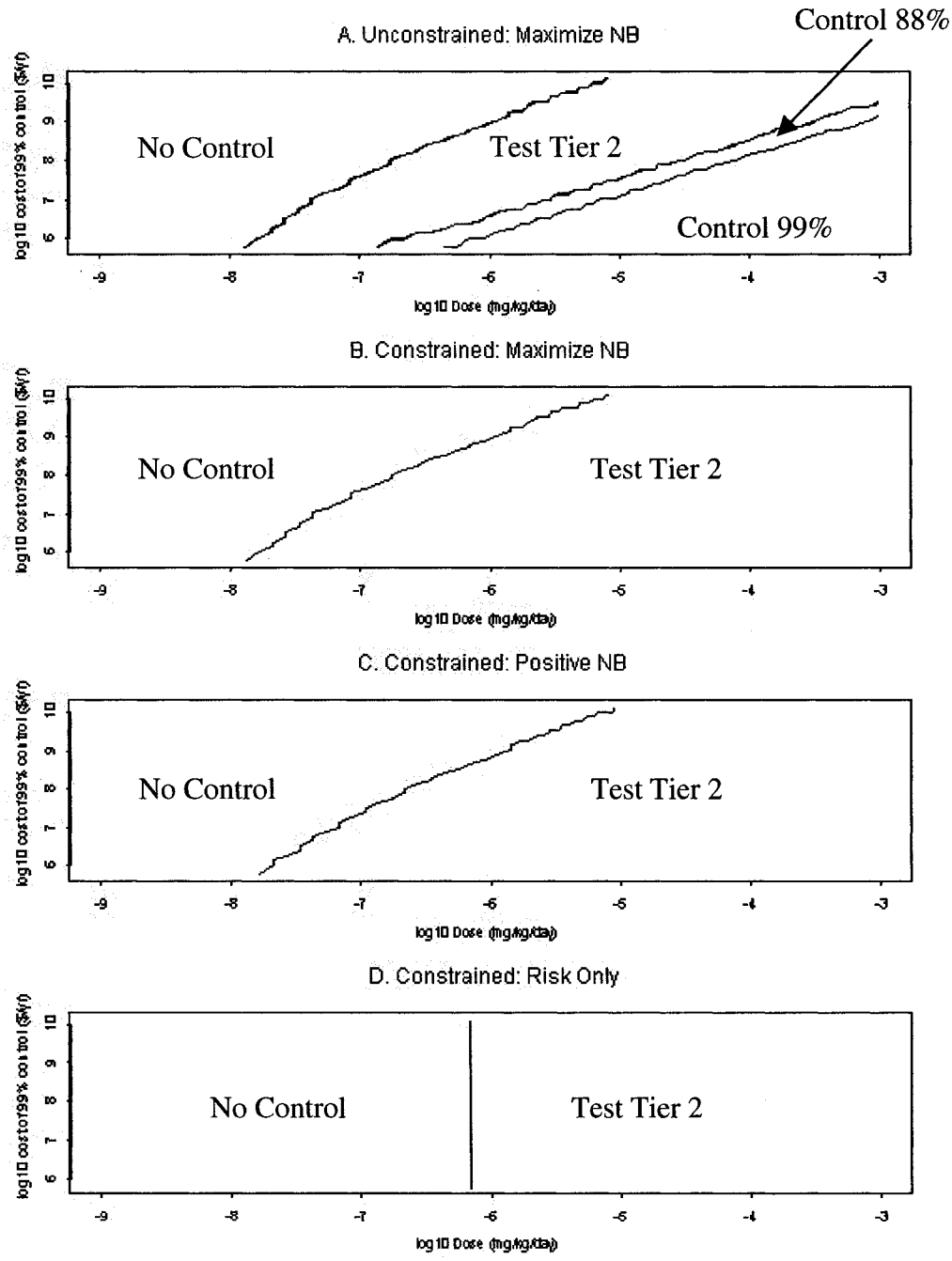

Figure 4.4: Foregone expected net benefits from regulatory restrictions

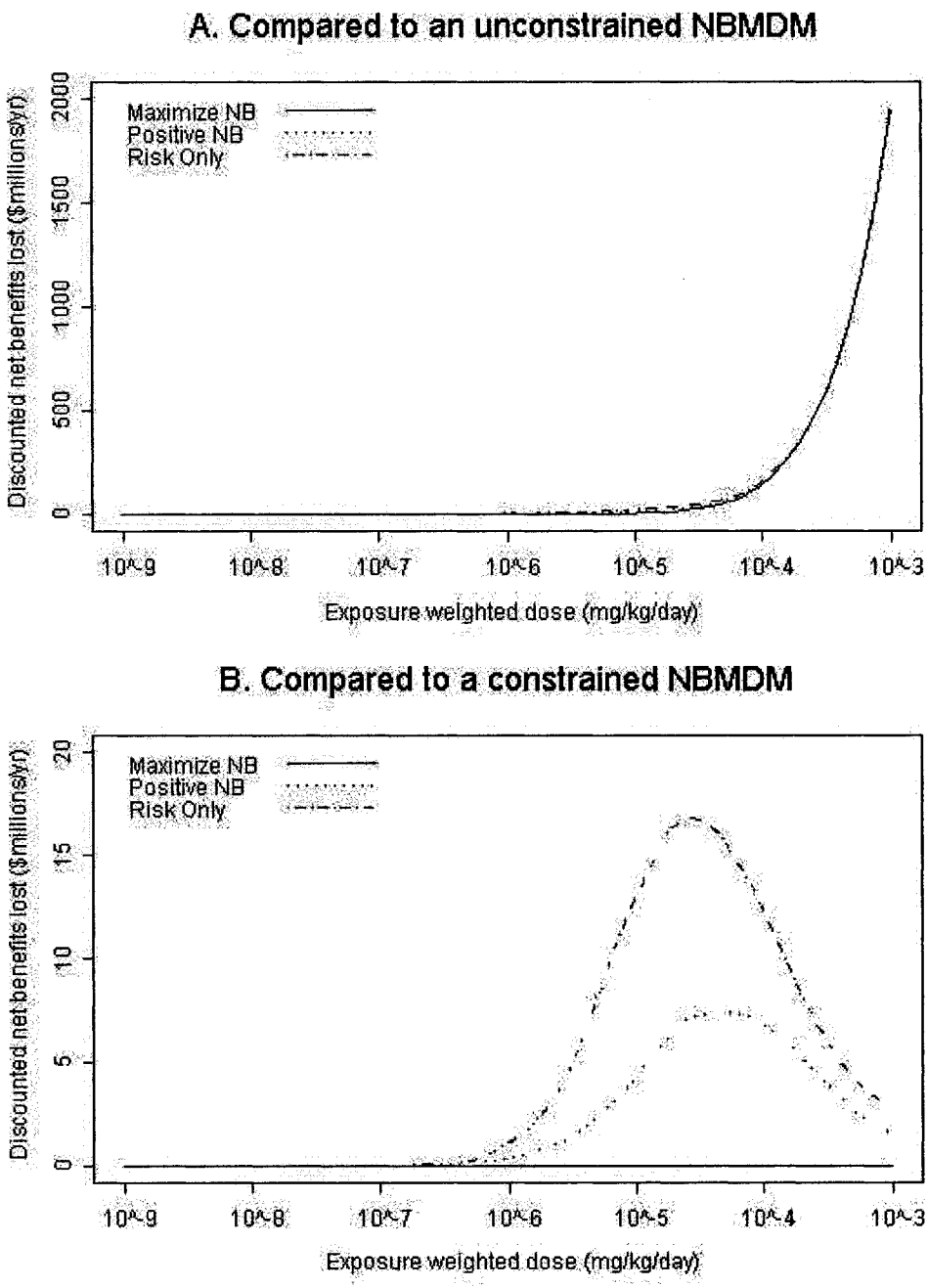

Figure 4.5: Difference in expected number of cancers prevented

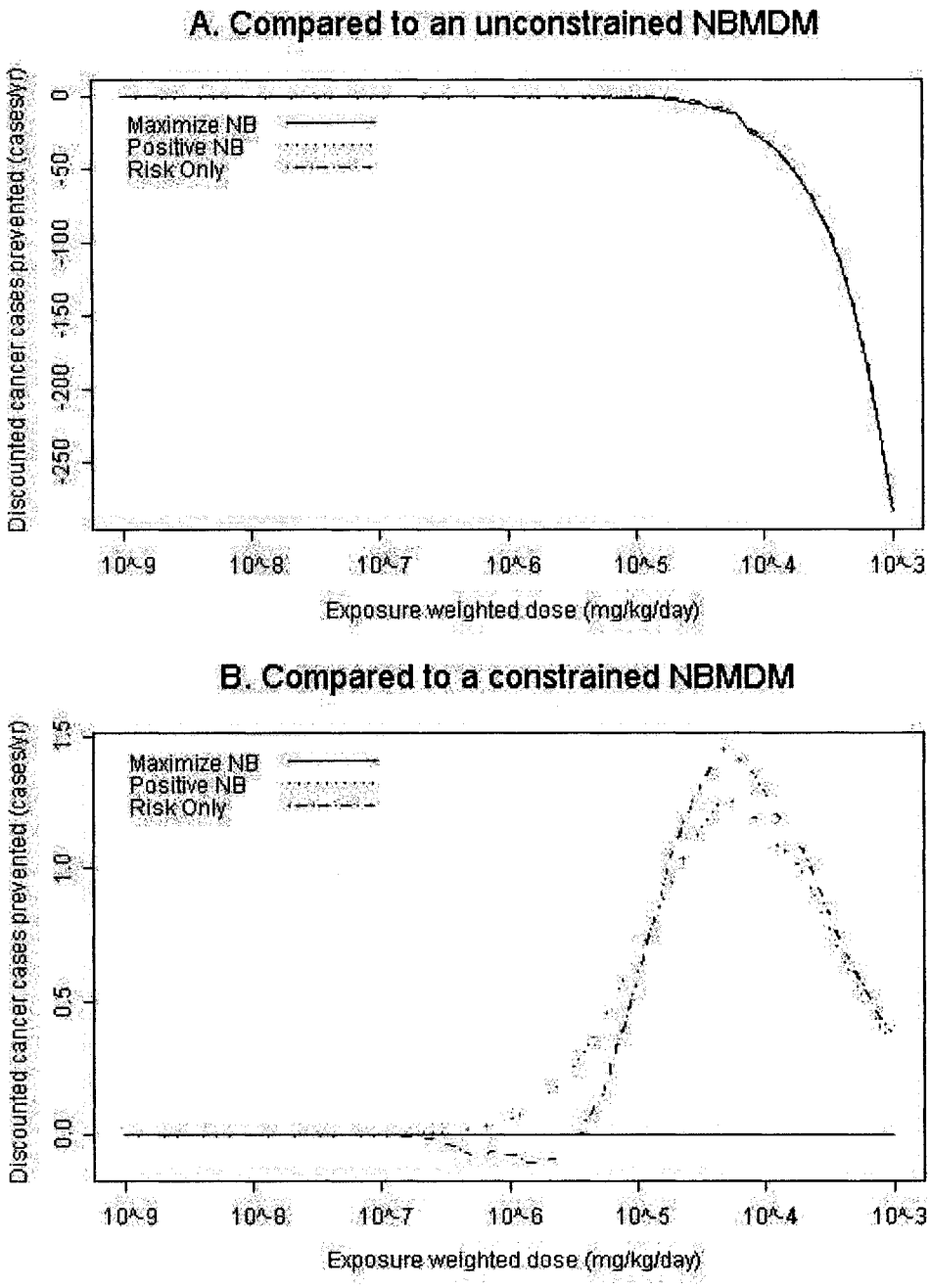

Figure 4.6: Difference in expected control costs incurred

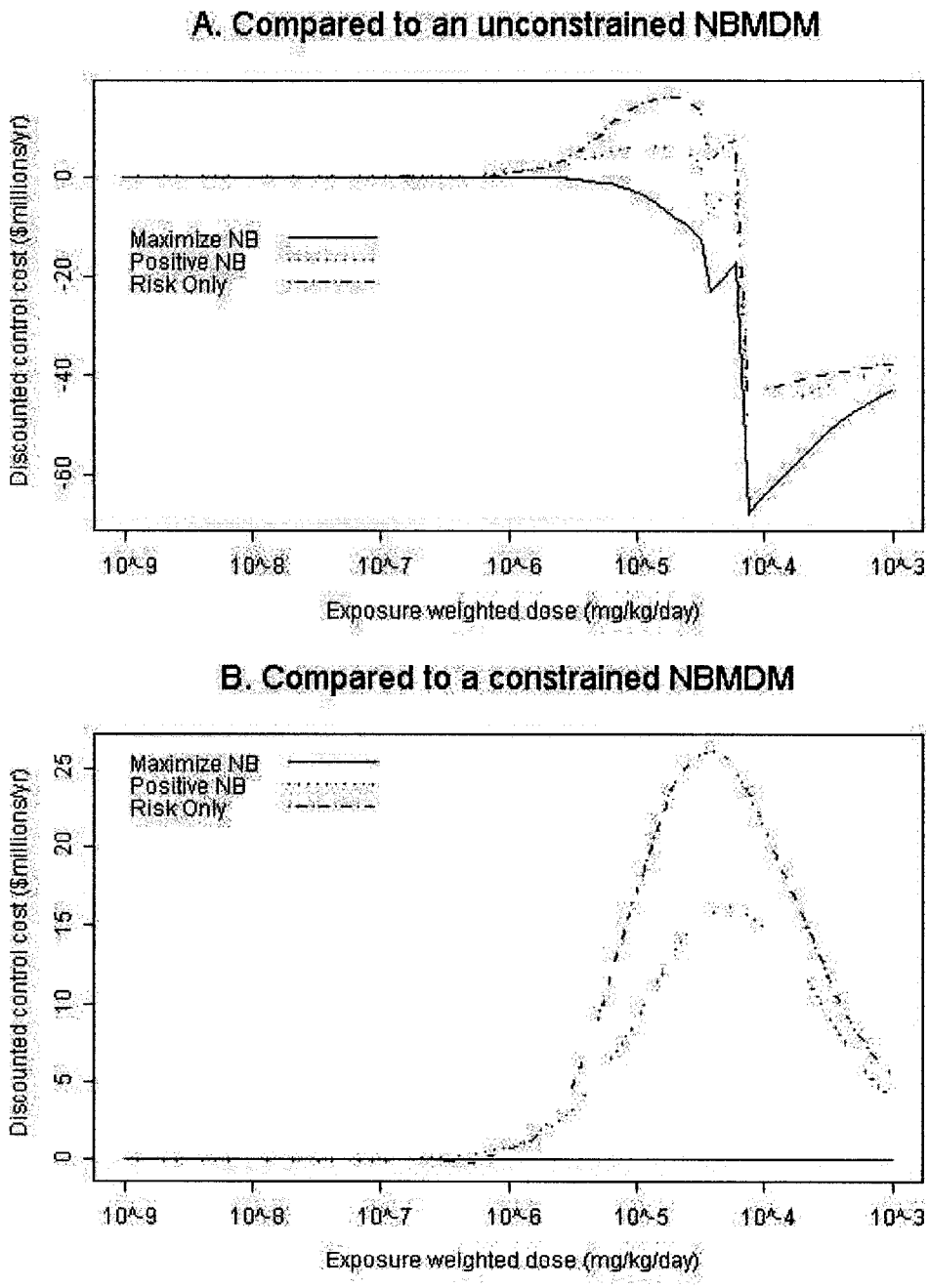

Table 4.2: Sensitivity of expected net benefits to changes in value of cancer prevented and discount rate

Expected value of net benefits ($/year) for different values of exposure weighted average dose (mg/kg/day)

	High VSL	Low Discount Rate	Base Case	High Discount Rate	Low VSL
VSL	$12 million	$7 million	$7 million	$7 million	$5 million
Discount Rate	5%	3%	5%	7%	5%
10^{-6} (mg/kg/day)					
Unconstrained	$3.07 million	$1.37 million	$1.20 million	$1.06 million	$0.63 million
Maximize Net Benefits	$3.01 million	$1.37 million	$1.19 million	$1.03 million	$0.63 million
Positive Net Benefits	$2.17 million	$0.91 million	$0.78 million	$0.68 million	$0.38 million
Risk Only	-$0.19 million	-$0.12 million	-$0.11 million	-$0.10 million	-$0.08 million
10^{-5} (mg/kg/day)					
Unconstrained	$91.0 million	$47.9 million	$45.1 million	$43.0 million	$28.6 million
Maximize Net Benefits	$79.3 million	$46.1 million	$40.7 million	$35.9 million	$26.2 million
Positive Net Benefits	$72.8 million	$40.7 million	$35.9 million	$31.7 million	$22.6 million
Risk Only	$46.0 million	$30.4 million	$26.8 million	$23.7 million	$19.1 million
10^{-4} (mg/kg/day)					
Unconstrained	$1,106 million	$603 million	$603 million	$603 million	$402 million
Maximize Net Benefits	$828 million	$529 million	$467 million	$413 million	$324 million
Positive Net Benefits	$822 million	$522 million	$460 million	$407 million	$317 million
Risk Only	$779 million	$515 million	$455 million	$402 million	$325 million
10^{-3} (mg/kg/day)					
Unconstrained	$12,424 million	$7,206 million	$7,206 million	$7,206 million	$5,118 million
Maximize Net Benefits	$9,059 million	$5,960 million	$5,260 million	$4,653 million	$3,741 million
Positive Net Benefits	$9,058 million	$5,959 million	$5,258 million	$4,652 million	$3,739 million
Risk Only	$9,012 million	$5,957 million	$5,257 million	$4,650 million	$3,755 million

Table 4.3: Sensitivity of the break point dose to changes in value of cancer prevented and discount rate

Break Point Dose (mg/kg/day) for testing decision after Tier 1

	High VSL	Low Discount Rate	Base Case	High Discount Rate	Low VSL
VSL	$12 million	$7 million	$7 million	$7 million	$5 million
Discount Rate	5%	3%	5%	7%	5%
No control vs. Test Tier 2					
Unconstrained	1.1E-07	1.7E-07	1.7E-07	2.2E-07	2.8E-07
Maximize Net Benefits	1.4E-07	1.7E-07	1.7E-07	2.2E-07	2.8E-07
Positive Net Benefits	1.4E-07	1.7E-07	2.2E-07	2.8E-07	3.5E-07
Risk Only	7.0E-07	7.0E-07	7.0E-07	7.0E-07	7.0E-07
Test Tier 2 vs. Control now					
Unconstrained	1.9E-05	7.7E-05	3.2E-05	2.4E-05	3.8E-05
Maximize Net Benefits	NA	NA	NA	NA	NA
Positive Net Benefits	NA	NA	NA	NA	NA
Risk Only	NA	NA	NA	NA	NA