What Toxicologists and Risk Assessors Think About Hormesis: Results of a Knowledge and Opinion Survey

WHAT TOXICOLOGISTS AND RISK ASSESSORS THINK ABOUT HORMESIS: RESULTS OF A KNOWLEDGE AND OPINION SURVEY

A Dissertation Presented

by

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Submitted to the Graduate School of the
University of Massachusetts Amherst in partial fulfillment
of the requirements for the degree of

DOCTOR OF PHILOSOPHY

February 2010
School of Public Health and Health Sciences
Environmental Health Sciences

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DEDICATION

To my sons Daniel and Nathan

ACKNOWLEDGMENTS

I would like to acknowledge and thank everyone who helped and mentored me along the way. I appreciate your supporting my desire to become a toxicologist after years of study and work as an engineer. You all understood and supported my heartfelt goal to understand and assess human health risk caused by environmental and workplace exposures and to play a role as a protector of human health and the environment.

I was fortunate to meet Dr. Edward Calabrese and that he accepted me into the Environmental Health Science Program. I am privileged to have been his student. I have learned so much from him and his dedicated and almost dogged inquiry into the phenomenon of the hormesis dose-response. I thank him for his extreme patience in accommodating my demanding work schedule as I worked in a similar almost dogged fashion to complete the requirements for a doctoral degree in Environmental Health Science. I would like to acknowledge the support, help and advice from my committee members Dr. Edward Stanek and Dr. Douglas Anderton. I also thank Dr. George Hoffmann from Holy Cross University. I appreciate all the hours of discussion and encouragement they provided in all phases of this study from survey instrument design, through data analysis and presentation of results.

The high quality of the survey instrument that assured the internal validity of this study could not have been achieved without the input from the twenty-five leading toxicologists, risk assessors and health physics professionals who donated their time, energy and know-how to review the instrument multiple times and provide valuable comments and criticisms. I thank you all.

I owe a great debt of gratitude to Shawn Douglas Lamb and the Society of Toxicology. The Society leadership and staff were enormously helpful and provided the very important comparative data without which this study could not have been completed and without which the external validity of this study could not have been achieved. In that same vein, I also acknowledge and thank Dr. Robert Lichter of the Center for Health and Risk Communication at George Mason University. His generous assistance in providing comparative demographic data from his concurrent survey of Society of Toxicology members gave me a wonderful opportunity to further evaluate the external validity of this study.

Thank you to my close friends, dedicated supporters that provided nearly continuous encouragement to overcome the difficulties of working extremely demanding jobs while pursuing my goal of becoming a toxicologist. To my more technically inclined friends, I appreciate the hours of discussion, exploration of ideas, and your reading and re-reading numerous versions of text. To my not so technical friends, thank you for indulging me while I spent so much of your time talking about my passion for investigating this very interesting dose-response concept called hormesis.

Finally, and most importantly I thank my loving, patient, and understanding family. I thank my sister Grace Donnell for her valiant encouragement. I thank my sons Daniel and Nathan for their never failing devotion; I dedicate this work to you both.

ABSTRACT

WHAT TOXICOLOGISTS AND RISK ASSESSORS THINK ABOUT HORMESIS: RESULTS OF A KNOWLEDGE AND OPINION SURVEY

FEBRUARY 2010

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Hormesis is a nonlinear dose-response characterized by biological responses at low doses that are opposite to those observed at higher doses. Studies and review articles on hormesis are being published at an increasing rate by researchers from diverse disciplines and debate has emerged over the role hormesis in risk assessment. As a result, a survey was conducted to assess toxicologists and risk assessors knowledge and attitudes about the hormesis dose response. Study goals were to: 1) ascertain attitudes towards hormesis and other dose-response models, 2) identify whether acceptance or rejection of hormesis is based on knowledge of hormesis, predisposing values, or demographic characteristics, and 3) evaluate potential for response bias. The survey consisted of 44 questions pre-tested by 25 toxicologists and risk assessors. The survey was distributed via email to the membership of the Society of Toxicology and the Society for Risk Analysis, 9,500 potential respondents. The overall response rate was 17% (n= 1,463) with a completion rate over 87%. Major findings were that 50% of respondents indicated sufficient data exist to support the view hormesis occurs across a wide range of species and endpoints, 59% indicated evaluating potential benefits due to hormesis

should be included in risk assessments, and 65% are in favor of modifying hazard assessment protocols to identify the presence of hormesis. Respondent characteristics such as: years of experience, society membership, education, residence, employment (excluding government and pharmaceutical companies), and political, economic or social views had little influence on opinion. One of the largest positive influences was experience with hormesis based on actual research; 79% of subjects who reported observing hormesis commonly in their studies agreed hormesis is broadly generalizable. The influence of non-response bias was evaluated through several internal and external measures. Despite a lower than hoped for response rate, but because of robust external validity measures, it is concluded that respondents' opinions are likely a reasonable representation of the societies of which they are members. Because this is a baseline survey, a follow-up survey is in order. Future survey design should separately evaluate the science of dose-response from the regulatory approach to risk assessment.

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CHAPTER 1

INTRODUCTION

1.1 Background and Purpose of Study

Hormesis is a nonlinear dose-response phenomenon characterized by biological responses at low doses that are opposite to those observed at higher doses, leading to either a J-shaped or inverted U-shaped dose-response curve. Evidence for hormesis has been published in the scientific literature from the late nineteenth century to the present (Calabrese and Baldwin, 1999; Henschler, 2006). Quantitative analysis of the hormesis dose-response curve began in earnest with the work of Calabrese and Baldwin (2001a). Their dose-response database provided the first analysis of the frequency in which the hormesis dose-response was reported in the scientific literature. This work was followed by additional frequency analyses and a description of the quantitative features of the hormesis dose-response (Calabrese and Baldwin, 2001a,b, 2002a,b; Calabrese and Blain, 2005). Results consistent with a hormesis dose-response were shown to be widely observed in medicine, molecular biology, pharmacology, nutrition, aging/geriatrics, agriculture, microbiology, immunology, exercise physiology and toxicology.

The data compiled by Calabrese and colleagues, coupled with numerous papers published by other researchers, indicate that hormesis is common, and highly generalizable across biological responses in numerous species, both plant and animal. In December 2007, when the concept for the present study was first developed, an examination of the PubMed® database, which indexes over 5,000 journals, listed 398 articles with the keyword hormesis that were published between 2000 through 2007.

Most articles presented original dose-response research for which the author(s) selected hormesis as a keyword. A summary of the types and content of a number of articles is included in the literature review in Chapter 2.

Despite the widespread reporting of hormesis research and the inclusion of the hormesis dose-response phenomenon into leading toxicological textbooks, hormesis as a model has not been adopted by regulatory agencies or recommended by science policy experts for conducting hazard assessments. In fact, the utility of hormesis for evaluating dose-responses from chemical hazard research has been and remains to this day intensely debated in the scientific literature of the field (Axelrod et al., 2004; Calabrese, 2005 a,b; Cook and Calabrese 2006a,b; Davis and Farland, 1998; Elliott, 2008a,b; Hoffmann, 2009; Holsapple and Wallace, 2008; Renn, 2008; Sandin, 2008; Thayer et al., 2006, 2005; Zapponi and Marcello, 2006).

Outside of the journal-based debate but weighing-in on the topic is the United States Environmental Protection Agency (EPA). In 2004, the agency implicitly rejected the use of the hormesis dose-response for conducting chemical hazard assessments and risk assessments. In a staff paper evaluating its risk assessment process, EPA stated that "as the purpose of risk assessment is to identify risk (harm, adverse effect, etc.), effects that appear to be adaptive, non-adverse, or beneficial may not be mentioned" (EPA, 2004). Furthermore, the EPA Guidelines for Carcinogen Risk Assessment (2005) state that "nonlinear approaches may only be used when data is sufficient to ascertain the mode of action and (emphasis added by EPA) the agent does not demonstrate mutagenic or other activity consistent with linearity at low doses". The guidelines indicate researchers must use the threshold model as the default model to derive a reference dose

(RfD) or reference concentration (RfC) when the dose-response is non-linear, thereby excluding hormesis altogether.

Because evidence of the hormesis dose-response effect is widely reported but still a matter of debate in the scientific literature, this study was undertaken and designed using the best available survey methodology to ascertain the prevailing attitudes, acceptance and reliance on hormesis as a scientifically valid concept among toxicologists and risk assessors.

1.2 Study Goals

The goals of this first-ever study of the hormesis dose-response concept among toxicologists and risk assessment professionals were to: 1) ascertain attitudes towards hormesis and other dose-response models, 2) identify whether the level of acceptance or rejection of hormesis is based on knowledge of hormesis, predisposing values, or demographic characteristics, 3) evaluate potential for response bias, and 4) establish research priorities for hormesis.

This study was designed to provide data that will aid in determining the status of hormesis as a dose-response concept accepted among toxicologists and to identify whether the level of acceptance or rejection of hormesis is knowledge-based or determined by predisposing values, demographic characteristics, and other factors.

Furthermore, it is hoped that the results will enable researchers and regulators to better understand the direction of toxicological research, hazard assessment, risk assessment, public health policy development and risk communication as it is influenced by views on hormesis and other dose-response models.

CHAPTER 2

REVIEW OF THE LITERATURE

2.1 Survey Methods

The review of survey methods relies strongly on the works of Tanur (1992) and Fink (1995). Development of sound surveys entails initially setting research objectives, followed by designing a research methodology to meet the research objectives, preparing a reliable and valid data collection instrument, administering the instrument, analyzing data, and reporting the results. Detailed implementation of the guidance provided by Tanur and Fink is described in Chapter 3: Study Methods. The following is a short review of survey principles adopted for this survey research on the hormesis dose-response.

2.1.1 Design

The survey instrument must be designed to maximize the validity and reliability of the research. The researcher must identify the target audience of the survey and develop relevant questions that are understandable to the target audience. Therefore, the researcher must fully understand the issues and the respondents before development of the questions. All ambiguous terms used in the survey's questions must be clarified and clearly defined. The survey researcher must assure to the best extent possible that the respondents have sufficient knowledge to answer the questions. This is usually done by pre-testing and pilot testing the instrument (Tanur, 1992).

In order to confirm the questions meet that goal they should be reviewed by subject matter experts and pre-tested by potential respondents. Ideally, survey questions

and statements should be short and easily read to minimize time on survey (Fink, 1995). The wording of the question should be such that it does not include biasing words and phrases and multiple phrases that relay more than one idea (Tanur, 1992).

2.1.2 Ascertaining Attitudes

Attitude is often used to mean opinion, belief, preference, feeling or value, and as a result, may be difficult to define and measure using a survey instrument. However scientific and technical methods are available for producing testing attitude scales that are valid for scientific survey needs. The ability of the questions to obtain information on attitudes is evaluated by subject matter experts during the design phase. Selection of pre-testers and pilot testers representative of the target audience is important. They must have enough knowledge about the subject to have an opinion about it, identify gaps in knowledge that warrant education or publicity, and help explain attitudes and behavior Tanur (1992).

2.1.3 Reliability Issues

A reliable survey instrument is one that is relatively free of both random and measurement error. Non-sampling error results from an imprecise definition of the target and study population and errors in survey design and measurement. A second non-sampling problem relates to definitions and inclusion and exclusion criteria. Definitions of key survey concepts should be based on best available theory and practice; pretests and pilot tests can help eliminate this problem Fink (1995).

Reliability is also impacted by response rate. Unsolicited surveys receive the lowest response rate. A 20 percent rate is not uncommon (Fink, 1995; Hamilton, 2003; Kaplowitz et al., 2004). Survey methodology must be sufficient to promote responses, minimize response bias, and reduce survey error. This is done by implementing a robust quality assurance system that keeps the survey responses confidential and anonymous and by identifying a sufficiently large number of survey recipients that are actually interested in or knowledgeable about the topic. Reliability is further improved by utilizing pretesting and pilot testing of questions during the survey design phase Fink (1995).

2.1.4 Validity Issues

Validity is the degree to which a survey instrument measures what it is purported to measure. The researcher must focus on assuring both external and internal validity. External validity refers to the extent to which the results of the study are generalizable. Internal validity answers whether the survey measures what it intends to measure and is tested by evaluating inter-item agreement within the survey (Litwin, 1995).

2.2 Hormesis

2.2.1 Background

One of the most common underpinnings of toxicology "the dose makes the poison" is attributed to Paracelsus, a 16th Century physician and scientist said to be the "Father of Toxicology". The saying demonstrates that throughout history many scientists

have well understood the complexities of biology that occur at low doses. In the 19th Century, the complexities of low-dose stimulation were evaluated in a series of experiments conducted by Rudolph Arndt and Hugo Schultz. They documented the occurrence of biological stimulation at low doses. Their documentation of the biphasic dose-response phenomenon is known as the Arndt-Shultz Law. However, their work was widely overlooked possibly due to its association with the controversial medical practice of homeopathy (Calabrese and Baldwin, 2000a). By the 1940's the biphasic dose response became known as hormesis, a term derived from the Greek word meaning "to excite" (Calabrese and Baldwin, 2000b). The historic development of the concept of hormesis and the corresponding belief that low doses of toxins could have stimulatory effects at low doses was detailed in literature reviews by Calabrese and Baldwin (2001c,d).

Prior to Calabrese and Baldwin's work, (Smythe, 1967) provided a compelling review of adaptive responses in the toxicological literature, but did not adopt the term hormesis. In his review Smythe points out that industrial hygienists were taught that the human body responds to acute changes with immediate re-adjustments and to repeated changes with adaptation. Smythe expressed concern that protective technological advances were producing a generation of people so protected from environmental changes that they would be less able to adapt to stress. The Smyth review, covering literature from 1922 through 1966, provides many examples of adaptive responses, increased growth, positive reproductive outcomes and increased longevity resulting from low dose exposures to chemicals and ionizing radiation.

2.2.2 Dose-Response Models

Evaluating, understanding, and applying concepts related to dose-response is the foundation of toxicology and is directly related to drug discovery and human health risk assessment. Two dose-response models, threshold and linear non-threshold (LNT), are traditionally used by regulatory agencies and other public health policy makers, as default models to describe the dose-response relationship.

The threshold model is used to assess risk posed by non-carcinogenic chemicals. It is based on the assumption that a threshold exists below which no adverse effects occur. Toxicological studies are designed to identify that threshold. The data yields a Lowest Observed Adverse Effect Level (LOAEL), No Observed Adverse Level (NOAEL), or Benchmark Dose (BMD) from which a "safe dose" is derived. Threshold model results are input variables, along with exposure data, for conducting human health and ecological risk assessments.

Regulatory agencies default to the LNT model to assess chemicals thought to be carcinogenic. The model assumes that if a large quantity of a chemical will cause cancer, then even a molecule poses a cancer risk (Calabrese and Baldwin, 2001c,d; Calabrese and Blain, 2005). The only case for which the LNT is not applied is when the chemical under study can be proven to have a non-genotoxic mode of action and the exact mode of action is known. Then the threshold model is applied (USEPA, 2005). The LNT model is carried out in 3 steps 1) high dose studies are designed and conducted to elicit a carcinogenic response, 2) data are evaluated to derive a point of departure (POD) near the low end of the observed range and 3) a curve is extrapolated from the POD to zero to derive a Cancer Slope Factor or Cancer Potency Factor that can be used to conduct a

human health risk assessment. The model assumes that biological response is directly proportional to dose without any threshold and that a negative response is always present down to the last molecule.

Neither the threshold nor LNT model evaluates data in the low-dose region of the dose response curve. The models were developed to fill in the data gaps that exist in the low dose range. These gaps exist because toxicological studies are typically designed with doses sufficiently high to assure the study produces an adverse effect, if one exists.

2.2.3 Hormesis as the Alternative Model

Traditional assumptions about the shape of the dose response continuum are challenged by the concept of hormesis. The hormetic dose response is a specific type of non-monotonic dose response characterized by low-dose stimulation and high dose inhibition. The curve is usually described as either J (U) -shaped or inverted J (U) – shaped where at low doses the response is opposite to that of high doses (Calabrese and Baldwin, 2001c,b; Calabrese and Blain, 2005). Calabrese and colleagues have developed two databases containing thousands of examples of hormesis. Collectively, the data demonstrate the hormetic dose response is more common than the threshold and LNT models in head-to-head comparisons and is generalizable across a broad range of toxic agents, organisms and health endpoints.

The first database contains almost 6,000 dose responses drawn from peer reviewed literature. In order to be included in the database, the study had to meet the following *a priori* entry criteria: 1) strength of study design including ≥6 doses with at least 3 below the NOAEL, 2) magnitude of stimulation, 3) statistical significance, and 4)

reproducibility of findings (Calabrese and Baldwin, 1997). Quantitative features of the dose responses in this database indicate hormetic stimulation (amplitude) is generally modest with approximately 80% of the responses showing a maximum stimulation approximately 30-60% greater than the control. The stimulatory range is much more variable than amplitude, and extends over a dose range of 20-fold or less (Calabrese, 2004a).

The second database was created to address frequency of hormesis in the toxicological literature. It included *a priori* entry criteria as well as *a priori* evaluative criteria (i.e. a well-defined NOAEL, ≥ 2 doses below the NOAEL, and the endpoint measured has the capacity to display either stimulatory or inhibitory responses). From this database, the frequency of hormesis reported in the literature was estimated to be approximately 40% (Calabrese and Baldwin, 2001c). This database was also used to assess which dose-response model, hormesis or threshold, occurred more often in the literature. The majority of dose-responses displayed values greater than the controls. The hormetic model was more common than the threshold model, suggesting that the hormetic model may occur 2.5 times more frequently than the threshold model (Calabrese, 2004b; Calabrese and Baldwin, 2003a; Calabrese and Blain, 2005).

In a comprehensive review of tumor cell literature, Calabrese found that hormesis occurred in over 130 tumor cell lines. The responses were produced by a wide range of agents including anti-neoplastics, non-neoplastic drugs, endogenous agonists, and phyto compounds (Calabrese, 2005b). Hormetic models in yeast data were observed 4 times more often than would be expected by chance alone (Calabrese et al., 2006).

Hormetic dose response relationships have been reported by other researchers specializing in immunology, pharmacology and dietary restriction. Dietary restriction is reported by Hayes (2006) as the most effective and reproducible laboratory intervention for extending lifetime survival in diverse organisms. Genome transcription analyses show the multiple effects antibiotics have on cells at low doses. All antibiotics, regardless of receptors and mode of action, exhibit the phenomenon of hormesis and provoke considerable transcription activation at low concentrations (Davies et al. 2006). It was proposed that many hormones and other biologicals have reverse effects in biologic systems depending on their dosage or concentrations and that characteristic may be useful for developing treatments for malignant tumors (Prehn and Berd, 2006).

The hormesis data are so convincing that this model was recently added to a leading toxicological text book, *Casarett and Doull's Essentials of Toxicology* (Klaassen and Watkins, 2003). The hormetic effects are hypothesized to occur when relatively low doses result in the stimulation of a beneficial or protective (adaptive) response, such as, receptor activity, modulation of DNA repair, the induction of detoxification enzymes, and/or the induction of cellular antioxidant defense systems (Calabrese, 2005c).

Evidence of hormesis is also reported in the epidemiological literature. Hormetic-like dose response relationships have been observed in the epidemiology literature (Mundt and May, 2001). However, Mundt and May concluded it was not possible to discern whether the observation was hormesis or rather the combined effect of several different biological or disease processes. They provide an example of the dose-response relationship between alcohol and all-cause mortality. Applying hormesis to this example however forces the definition to include dose response relationships that incorporate

diverse causes of mortality and disease mechanisms. Literature reviews support the hypothesis that hormesis is caused by diverse adaptive response mechanisms (Cook and Calabrese, 2006a).

The evidence for the hormesis dose-response model and the argument the dose-response is caused by diverse adaptive biological responses, is strengthening due to ongoing mechanistic research performed for drug development. A single mechanism for hormesis has not been identified; however, it appears to operate within a mechanistic framework that is designed to conserve resources. It may prove to be a modest overcompensation to a slight disruption in homeostasis (Calabrese, 2004b). Research studies in biological systems have identified dozens of receptor systems that reliably demonstrate the hormesis dose response (Calabrese and Baldwin, 2003b; Hadley, 2003).

The significant experimental evidence compiled by Calabrese and others, supports the conclusion that the hormetic dose responses are broadly generalizable, and are independent of biological model, endpoint measured, and stressor agent.

CHAPTER 3

STUDY METHODS

3.1 Introduction

This chapter presents a description of all study procedures and methods, including selection of the survey target population, development of the survey instrument, survey administration, and data analysis.

3.2 Identification and Selection of Survey Target Population

The goal of the study is to ascertain expert opinion and attitudes about various dose-response models, particularly hormesis, and to determine the characteristics of those who would, if permitted by the regulatory framework, take the hormesis dose-response into account when designing or interpreting risk assessments. Therefore, professional societies whose members are known to specialize in toxicology and risk assessment were chosen for the study. The target societies were the Society of Toxicology (SOT) (n=approximately 5,800) and the Society for Risk Analysis (SRA) (n=approximately 3,500).

Solicitation of participation from each society and access to the membership lists are described below. A discussion of the impact of participation, or lack thereof, by the membership of the societies on the overall study results is provided in Chapter 5: Discussion of Study Results.

3.2.1 Society of Toxicology

3.2.1.1 General Description

The Society of Toxicology provides the following description on the public access portion of its website www.toxicology.org . "The Society of Toxicology (SOT) is a professional and scholarly organization of scientists from academic institutions, government, and industry representing the great variety of scientists who practice toxicology in the U.S. and abroad. SOT is committed to creating a safer and healthier world by advancing the science of toxicology. The Society promotes the acquisition and utilization of knowledge in toxicology, aids in the protection of public health, and facilitates disciplines. The Society has a strong commitment to education in toxicology and to the recruitment of students and new members into the profession".

The Society of Toxicology offers several types of membership: Full, Associate, Postdoctoral, Graduate Student, and Honorary. In order to become a full member, a toxicologist must have a defined number of years of relevant toxicology experience depending on highest degree obtained and sponsorship including letters of endorsement by three full members. The application is then voted on by members of the SOT council and Membership Committee. The requirements are less stringent for Associate, Postdoctoral, and Student memberships, but all must demonstrate professional scientific activities in toxicology or be enrolled in a graduate degree program and be accepted by the membership committee. The Society consists of approximately 5,800 members overall who have a broad range of toxicological interests including, but not limited to, the areas of specialization selected for the demographics portion of this study's

questionnaire. This information on SOT member qualifications is important to understand for analysis of SOT responses.

3.2.1.2 Obtaining the Membership List

The Society was requested to endorse the study in a letter dated June 20, 2008. Society administrative staff indicated that the request would take several months to process because it would have to be approved by a newly formed Research/Meeting Sponsorship Committee. The committee was not scheduled to meet until September 2008. SOT administrative staff indicated that because this researcher is a full member of the society it would be more expeditious to obtain the needed email addresses from the membership directory. Therefore, the email addresses were obtained by downloading the membership directory from the SOT website. The directory is only available to members using a society provided password. The email distribution list that was downloaded onto the University list-serve consisted of 5,833 distinct email addresses. This list includes all members according to SOT administrative staff.

3.2.1.3 Obtaining Society Demographics for Comparing Study Respondents to Society Membership

The representativeness of the survey research study population can be indirectly evaluated by comparing survey respondents' demographic characteristics to the overall demographic characteristics of the complete population list of the Society. After several discussions with Society administrative staff followed by a formal request letter, the Society provided summary statistics on the membership demographics. A copy of the

request letter is provided in Appendix A. The data provided by SOT included the following information about members: gender, education, years of experience, and primary specialty. The Society obtained the membership data from their annual online membership renewal forms. The society does not mandate that members provide demographic information; it is voluntary.

3.2.2 Society for Risk Analysis

3.2.2.1 General Description

The Society for Risk Analysis (SRA) provides the following self description on the public access portion of its website www.sra.org . "The Society for Risk Analysis is an international interdisciplinary professional society devoted to risk analysis. Members have interests in risk analysis, risk perception assessment, risk management and risk communication. The interdisciplinary make-up of the society is aimed at addressing, in an integrative way, emerging issues in risk analysis. SRA consists of members who specialize in assessing health, ecological and engineering risks and natural hazards. The society also explores policy, social and economic implications of risk issues. SRA membership recruitment is targeted at a wide range of institutions including federal, state and local governments, industry, academic institutions, not-for-profit organizations, law firms and consulting groups. SRA members include Risk Analysts, Ecological and Environmental Scientists, Emergency Preparedness and Response Planners, Engineers, Health Scientists, Government and Regulatory Officials, Journalists, Lawyers, Natural and Physical scientists, Policy Analysts, Public Administrators, Safety officers, Social and Behavioral Scientists, Toxicologists, and Transportation and Infrastructure scientists.

The Society offers its approximately 3,500 members an opportunity to join any of the following specialty groups: 1) Biological Stressors, 2) Decision Analysis and Risk, 3) Dose Response, 4) Ecological Risk Assessment, 5) Economics and Benefits Analysis, 6) Engineering and Infrastructure, 7) Exposure Assessment, 8) Risk Communication and 9) Risk Science and Law."

3.2.2.2 Obtaining the Membership List

The Executive Director of SRA did not respond to written requests, emails, or phone calls. The email list was therefore, obtained from the online membership directory available to members using a Society provided username and password. The email distribution list that was downloaded onto the University list-serve consisted of 3,542 distinct email addresses.

3.2.2.3 Obtaining Society Demographics for Validity Analysis

The SRA did not respond to repeated requests for comparative demographic information. The impact of the lack of comparative data is discussed in Chapter 5: Discussion of Results.

3.3 Selection of a Census Survey

A complete census survey, in which the entire population is provided an opportunity to participate, was selected as the design for this study. Use of a census survey eliminates concerns about potential sampling bias associated with non-probability

sampling methods. The concern with a census survey is the potential for non-response bias.

3.4 Development of the Study Survey Instrument

3.4.1 Choice of Response Category (Dichotomous vs. Likert scale)

The initial drafts of the survey instrument were developed using 5 point Likert Scale response categories following the convention of placing the negative end of the scale first. Numbers were assigned to the ordinal data ranked lowest to highest. However, it could not be determined based on the Likert Scale how participants with a negative (low) opinion of hormesis quantitatively compared to people with slightly negative, a neutral, positive (high), or highly positive opinion of hormesis. The assumption that Likert scales could be treated as ordinal categories did not prove correct for this study. Subjective hence arbitrary decisions would have had to be made about how to re-code the data for logistic regression analysis. Thus, the survey was re-written to accommodate dichotomous responses that would not require re-coding.

During the pre-testing and pilot testing of the questionnaire, some reviewers suggested use of a Likert Scale because they felt dichotomous responses did not give respondents with neutral opinions a response option. This suggestion was not adopted due to concerns about subjective and arbitrary re-coding of the responses.

3.4.2 Questionnaire Development

The process for revising and creating a valid and reliable survey instrument includes 1) initial question development, 2) pre-testing and revision, and 3) pilot testing and revision (Fink, 1995; Tanur, 1992).

The goals for developing a valid questionnaire for the study were the following: 1) make the questions concrete, precise and unambiguous, 2) assure each question conveyed one thought, 3) eliminate potential for biasing the respondent, 4) develop a questionnaire that could be answered in less than 20 minutes to keep attrition low, and 5) assure validity and reliability of the survey instrument.

3.4.3 Questionnaire Documentation

The survey was pre-tested and pilot tested by 25 toxicologists and risk assessors representing diverse backgrounds and employment. After committee review and revision, the survey instrument was Beta tested by an independent third party Professor of Genetics, Toxicology, and Botany at Holy Cross University. The suggested revisions were to reduce the number of questions and re-word certain questions to assure clarity of meaning. The revised questionnaire was submitted to four pre-testers. The four were selected based on their diverse areas of expertise; specifically, general toxicology, pharmacology, pharmacokinetics and health physics. Their suggestions for wording changes were adopted. None of the reviewers made substantive content changes. The questionnaire was then provided to twenty toxicologists and risk assessors for pilot testing. This group consisted of professionals with advanced degrees and represented all professional employment sectors of the target population. The pilot test reviewers were

asked to validate the assumption that the survey could be completed in the desired timeframe. They were also requested to recommend questions for inclusion or deletion and to evaluate questions for meaning. Specifically, they were asked to evaluate whether the questions and statements were clearly written, easy to understand, appropriate to the audience and unbiased. They were also asked to provide suggestions for additional content and improvement of content. Although the pilot study was carried out by 20 reviewers, only 12 provided specific written comment. The comments were focused on clarifying the meaning of specific questions.

3.4.4 The Final Survey Instrument

The final survey instrument consisted of the following:

- Section 1: Introduction Cover Letter and Informed Consent
- Section 2: Demographic Data
- Section 3: Knowledge and Attitudes about Interpreting Dose-Response Assessments
- Section 4: Knowledge and Attitudes about the Hormesis Dose-Response
- Section 5: Knowledge and Attitudes About Risk Assessment Principles and Practice
- Section 6: Conclusion and Request for Feedback

3.4.4.1 Section 1: Introduction and Cover Letter

Enticing respondents to complete the survey is critical to increasing response rate and therefore improving survey validity. An invitation email accompanied the request to

participate and survey link (Appendix B). The survey instrument Introduction section repeated the purpose and goals as well as contained the informed consent notification. The email subject line was worded so that the potential respondent would understand that the subject matter was hormesis. The email invitation and Introduction incorporated the following as recommended by Fink (1995):

- Explain the purpose of the study
- Describe who is conducting the study
- Explain how respondents were chosen
- Provide a realistic estimate of time to complete the survey
- Explain how confidentiality will be protected
- Provide the response deadline
- Provide instructions for completing the survey
- Provide researcher contact information
- Provide examples of how the data will be made available to the respondents
- Provide the informed consent

3.4.4.2 Section 2: Demographic Data

While the concept for this survey was being developed, it was thought that a respondent's knowledge and opinions about risk assessment in general and hormesis in particular may vary by gender, age, education, experience, type of employment, specialty and subspecialty, as well as social, economic, and political views, and these variables were taken into account with the final selection of demographic variables for analysis. Further, four of the five research goals depend on obtaining and interpreting respondent

demographic data. Demographic variables were chosen based on the research goals of identifying characteristics of respondents which may influence attitudes towards hormesis when interpreting risk assessment results, and in order to be inclusive of a wide variety of employment areas and specialties in toxicology that could be used in the analysis.

The survey was designed to keep attrition rates as low as possible by placing the request for demographic information at the front of the survey (Andrews et al., 2003; Fink, 1995).

3.4.4.3 Documentation of Final Subject Matter Questions

The knowledge and opinion questions are contained in Sections 3, 4 and 5. In order to assist the respondent in answering the questions figures depicting the linear non-threshold, threshold, and J-shaped hormesis dose response curves were inserted at the beginning of each section. Documentation of each question and the purpose for asking the question is presented in Appendix C.

3.4.4.4 Final Questionnaire

The final version of the questionnaire contained 46 coded statements, including a question at the beginning asking the participant if he/she had taken the survey before and 2 open-ended questions at the end of the survey instrument asking the participant for comments on missed content and survey quality. The first question "If you have taken this survey before, please skip to the end" was added because respondents could have been sent two different survey links if they were members of both SOT and SRA. If the

person answered yes to question 1, they were sent to the end page thanking them for their participation.

3.5 University of Massachusetts Human Subjects Requirements

This study was carried out in compliance with 45 CFR 46 and guidelines set forth by The University of Massachusetts Human Research Protection Office (HRPO). The office assures protection of the rights and welfare of human subjects in accordance with federal regulations and the campus Federal Wide Assurance issued by the U.S. Department of Health and Human Services. The study was approved by the Internal Review Board (IRB) on August 22, 2008. The study qualified for expedited review within the School of Public Health because it involved no more than minimal risk to subjects. The review was coordinated by Linda Downs-Bembury and Dr. Richard Van Emmerik.

3.5.1 IRB Form and Training

The Abstract of Research Plan, Form ADM 441 and Cover Letter submitted to the IRB are archived in this researcher's academic record. The required training in protection of human subjects was completed on October 14, 2007 including the required training module for "Social and Behavioral Research Investigators and Key Personnel" and the optional training module for "Internet Research." The Collaborative Institutional Training Initiative (CITI) completion certificate is archived in this researcher's academic record. The training was invaluable in assuring the questionnaire was designed to comply with the Belmont Principles of respect for persons, benefice and justice.

3.5.2 Informed Consent

Federal requirements followed by the University require that investigators conducting human research obtain the consent of the subject. The purpose of informed consent is to educate potential respondents about the purpose of the study, research procedures, and risks and anticipated benefits of participation. The informed consent was included in the Introduction section of the survey. The purpose, risks and benefits of the survey were explained. The respondents were assured that their responses would be confidential and anonymous. They were offered an opportunity to ask questions and were provided this researcher's telephone number and email address. Potential respondents were informed they could withdraw from the survey at any time and could choose not to answer all questions. Accordingly, the web based survey did not force the respondent to answer a question before proceeding to the next question.

3.5.3 Privacy and Anonymity

Protecting privacy is paramount when conducting survey research. Web-based surveys provide researchers more opportunity to inadvertently violate privacy than in conventional surveys. For example, email pre-notification, the survey itself, and follow-up could be considered unsolicited "spam". The goal is to build trust to encourage people to participate so they do not feel "spammed" or exploited. Therefore, the survey was delivered through the University list-serve from this researcher's personal email address.

Because the survey was being sent to a broad range of potential respondents, including government employees, it was designed for all responses to be anonymous,

thus eliciting candid answers. All respondents were assigned a survey ID number through the web-based survey tool. The tool's database recorded the ID tagged to a specific email address and the survey was entered by a link embedded in the email. By separating the survey from the email, privacy issues around email (work monitored email, multiple users having access to password protected email accounts) were minimized.

The only respondents who could be personally identified are those who contacted me personally to ask questions or make comments. Even in such a situation, their responses remained anonymous because they were maintained in the separate third party database. Protection of privacy is further discussed in the following section, survey administration.

3.6 Survey Administration

3.6.1 SurveyMonkey®

The SurveyMonkey ® tool was chosen for survey administration because 1) there is extensively documented research indicating that it protects respondent privacy and anonymity, and 2) respondents may have familiarity with this tool because it is used extensively by professional societies to administer opinion surveys and for distributing ballots for voting on candidates for various society and specialty section elections.

The weblink "collector" provided by SurveyMonkey ® for each distribution list allowed only one response per unique link and enabled IP address blocking so the survey could not be sent from the recipient to others who were not members of either SOT or SRA. SurveyMonkey® has established a strong privacy policy and anti-spamming

agreement. Therefore, the email and survey link contained an "opt out" remove link field so that reminders would not be forced upon an unwilling recipient.

3.6.2 Distribution and Reminders

Separate email list-serve distribution lists were established for each of the two societies. The survey was distributed via email to 9,375 potential respondents, all of whom were members of either the Society of Toxicology (n=5,833) or the Society for Risk Analysis (n=3,542). The initial invitation to participate was emailed on August 26, 2008. Reminders were sent on September 9th and September 24th. The survey closed on October 7, 2008.

3.7 Data Analysis

3.7.1 Introduction

The goal of the data analysis was to identify relationships between variables, to make comparisons between demographic groups and other logical groupings of variables, and ultimately to determine how acceptance or rejection of hormesis relates to knowledge of the subject, predisposing values, or demographic characteristics. The analysis for this study was carried out in several stages as described below.

3.7.2 Data Management and Variable Codes

Descriptive statistics provided by SurveyMonkey ® were downloaded and are summarized in tables in Chapter 4. The raw data were downloaded from

SurveyMonkey® as comma separated value (CSV) ASCII text files. SAS software, version 9.2 SAS Institute, Inc, Carey, NC was used to convert the CSV files into a single SAS data set containing all question responses, comments, and metadata, such as survey start and end times and the unique respondent ID assigned by the SurveyMonkey ® tool. Data management included the following:

1) Removing invalid responses and duplicate survey returns. SurveyMonkey ® retains a record of everyone who opened the survey but did not answer any questions. These subjects were removed from the database prior to any analysis. Because a respondent could have received the survey from both distribution lists, as described above, duplicate survey returns were removed by treating returns with identical gender, state of residence, and date of birth as a duplicates.
2) People who completed the demographic portion of the survey and answered at least one of the first five questions in Section 3 were categorized as respondents.
3) Logical groupings of demographic characteristics were developed to facilitate analysis. Examples include, but are not limited to, work experience categories (based on years of experience), employment type (e.g. industry, academia, and government), and specialty type (e.g. combining reproductive and developmental specialties).
4) Additional variables were created for time spent on survey by the study participant and whether a respondent completed the survey. The survey was considered complete if the respondent answered any of the last four survey questions.

3.7.3 Descriptive Statistics

Respondent characteristics of all validated data were summarized for all demographic variables, type of employment and specialty. Overall response rate and response rate by society membership were calculated. Completion rate was calculated by the key demographic variables of gender, professional society membership and education.

3.7.4 Univariate and Joint Analysis

The textbook *Biostatistics: A Foundation for Analysis in the Health Sciences* (Daniel, 1995) and the SAS Procedures Guide, Version 6, Third Edition (SAS, 1990) served as the basic foundation for identifying the appropriate statistical tests to apply to the data. Odds ratios (OR) with 95% confidence intervals (CI) estimated through logistic regression analysis were used to identify demographic characteristics of those who accept/reject hormesis and to identify the characteristics of subjects most likely to use hormesis for risk assessment.

3.7.4.1 Tests for Association

The chi-square test statistic was used to compare frequencies for categorical variables (Daniel, 1995, p. 516). The test chi-square test compares observed frequencies to expected frequencies. Examples of null hypotheses for this study are: no difference between male and female respondents, no difference between educational categories, and no difference between various employment categories. The chi-square output was

scanned to identify significant ($p<0.05$) heterogeneity in responses among and between demographic variables.

3.7.4.2 Univariate Analyses of Associations

The variables that were found to be statistically significant across most questions were further evaluated by calculating odds ratios to examine the odds that a category of respondents agreed or disagreed with the idea asked by the policy questions described below. Frequency data were entered into 2x2 tables. Respondents were dichotomized (e.g. male/female, SOT/SRA, EverEPA/All other employers) with respect to whether they agreed or disagreed with the question. The OR along with its 95% CI was calculated using standard methods (Daniel, 1995, p.547).

Evaluation of statistical significance was accomplished by examining the upper and lower bounds of the 95% CI. If the lower bound of the CI was >1.0 or the upper bound was <1.0, then the estimated odds ratio was deemed statistically significantly different from the null odds ratio of 1.0.

3.7.4.3 Multivariate Analyses

The logistic regression model is employed when the dependent variable is dichotomous. Logistic regression allows one to estimate the ORs for several variables of interest, permitting the identification of variables that remain significantly associated with the dependent variable when adjusted for the effects of other candidate covariates. It is the most widely used statistical model for evaluating several characteristics which

are independently associated with a particular dichotomous outcome (Daniel, 1995, p. 484).

Logistic regression modeling was carried out only on the questions of interest described below. For those questions ORs with upper and lower bounds satisfying the criteria for statistical significance were included in a logistic regression model to determine the characteristics associated with the "agree" response in a multivariate analysis. A step-wise model was developed for variables that might be highly correlated such as the general categorical variable employment at a regulatory agency and specific categorical variable employment at the USEPA.

3.7.5 Selecting Specific Questions for Univariate and Multivariate Analysis

All questions in the survey instrument are important for gaining an understanding of respondents overall knowledge and opinions about risk assessment and the hormesis dose-response. Four questions were singled out for detailed analysis because they provided answers to the specific research question regarding who would take hormesis into consideration when designing or interpreting risk assessments. The selection of four "policy questions" is described below.

The first policy question is number 32. It covers the basic tenants of review papers and original research published by Calabrese and others that sufficient data exist to suggest hormesis occurs in a wide range of species and endpoints following low-dose exposure to a broad range of chemical agents and physical stressors.

The second policy question is number 36. It was designed to evaluate whether hormesis could be accepted in risk assessment to obtain potential benefit. This question

is meant to get to the heart of the hormesis debate detailed in Chapter 2: Review of the Literature. Question 36 was also selected for comment analysis. An *a priori* concern of the research committee was that only people with a strong positive or negative opinion about hormesis would take the time to answer a detailed questionnaire on the topic. This question was selected for comment analysis because EPA guidance specifically states benefit cannot be taken into account when determining a safe dose (EPA, 2004) thus, this question more than the others could have elicited a "passionate" comment.

The third policy question is number 38. Many regulations in place today are based on the linear non-threshold and threshold dose-response models. Question 38 asks the respondent to consider a situation in which hormesis is the default model for risk assessment. The question serves as an important indicator of the impact hormesis could have on the regulatory framework.

The fourth policy question is number 39. This question asks the participant to consider the current state of knowledge about hormesis and provide an opinion as to whether the phenomenon justifies a change in hazard assessment methodology. The question is an important indicator of the impact hormesis could have on the design of dose-response experiments.

In addition to the four policy questions, there was also interest in evaluating how respondents with direct experience in dose-response research and who reported observing one or more of the various dose-response curves pictured in the questionnaire, viewed the four policy questions. Therefore the response to question 26 which asks a respondent to report how commonly he/she has observed hormesis was compared with whether the respondent agreed to questions 32, 36, 38 and 39.

3.7.6 Internal Consistency Analysis

Measures of internal consistency answer whether the survey measures what it intends to measure. It is tested by evaluating inter-item agreement within the survey. Chronbach's Coefficient Alpha is a statistical measure of internal reliability commonly used to assess survey instruments. It is applied to groups of questions designed to measure different aspects of the same concept. Although single items may be quicker to administer, the data set is richer and more reliable if several different items are used to gain information about a particular attitude or opinion (Litwin, 1995). The calculation of Alpha statistical test to evaluate internal consistency was carried out using standard equations and procedures (SAS Procedures Guide, 1990).

Two tests for internal consistency were built into the questionnaire. The following questions were designed to take one or more measures on the subject's attitude or knowledge about a particular risk assessment, policy or hormesis topic. The first test was disagree response to question 15 vs. an agree response to question 19. Both evaluate the respondent's opinion on the current dose response default model for cancer risk assessment. The second test was agree response to question 31 vs. an agree response question 41. Both indicate whether the respondent shows a consistent understanding of J-shaped dose-response curve depicted in the figures.

3.7.7 Evaluation of Response Bias

In order to address concerns about response bias the characteristics of those who completed the survey were compared to those who dropped out along the way. Chi-

square tests were used to identify statistically significant differences by demographic variable.

Auxiliary information provided by SOT was used to compare the overall demographic characteristics of the entire membership of the society to the demographics of study respondents. This analysis was also used as an indirect assessment of external validity in assessing whether the survey results may be generalizable to the survey target population and participating societies.

An independent study provided by researchers conducting a similar survey on the SOT membership three months after the present survey was also used to evaluate validity of overall study results.

The research committee suggested coding comments to Questions 36, 45 and 46 as to whether they were negative, neutral, or positive toward hormesis in an effort to indirectly evaluate response bias. It is acknowledged that this coding is subjective. For the purposes of this study, if comments were overwhelmingly positive or negative, over 20% in either direction, it was concluded response bias could be present. If however, the overwhelming majority of comments, 80%, were neutral then it was concluded response bias may be low.

CHAPTER 4

RESULTS

4.1 Introduction

This chapter presents the study results. The order of presentation follows the methods outlined in Chapter 3, beginning with summary of response rate, completion rate, respondent characteristics, and descriptive statistics for each question. This is followed by univariate and multivariate logistic regression analysis of the four policy questions and the dose-response research question, internal consistency analysis and evaluation of potential response bias. Interpretation and discussion of findings are in Chapter 5.

4.2 Descriptive Statistics

4.2.1 Response Rate

The internet survey invitation link was sent via email to 5,833 Society of Toxicology members and 3, 542 Society for Risk Analysis members. SurveyMonkey® recorded a total of 1,882 potential respondents opening the email link. Of that number, 1,326 opened the SOT survey link providing an overall response rate of 23%; and 556 opened the SRA survey link providing an overall response rate of 16%. All 1,882 responses were downloaded into the SAS database as described in Chapter 3. The questionnaires with missing data (n=221) and duplicates (n=15) were removed. The low number of duplicates suggests few respondents attempted to answer the survey more than once as a result of receiving two invitations, one from each of the two distribution lists.

The adjusted response rates after missing and duplicates were removed are 20% and 14%, respectively. A total of 183 subjects completed the demographic portion of the survey, but did not answer the remaining questions. These 183 subjects tended to be female (14% were female vs. 8% who were male), belong to the Society for Risk Analysis (14% were members of SRA vs. 10% who were members of SOT), and have less experience (16% had 0-9 years of experience vs. 5% who had over 30 years of experience). The response rate adjusting for people who stopped the survey after the demographics section was 18% (n=1, 045) for SOT and 12% (n= 418) for SRA. Overall and adjusted response rates are presented in Figure 4.1. Subjects who completed the demographic questions and answered at least one of the first four subject matter questions (questions 14 -17) were classified as respondents. Twenty-three email addresses (6 for SOT and 17 for SRA) were returned as undeliverable. This was not enough to materially affect the response rate for either society. The list-serve recorded over 200 bounces, automatic replies such as out of office indicators. These bounces were not considered undeliverable in calculating response rate because it is possible that the subject could have eventually opened the survey link and answered the questionnaire, provided they returned to their email prior to survey close on October 7, 2008. Because the survey was anonymous, it is not known whether the bounced email recipients answered the questionnaire.

Most respondents completed the questionnaire on or near the dates of the initial invitation or on or near the dates of the reminders as shown in Figure 4.2.

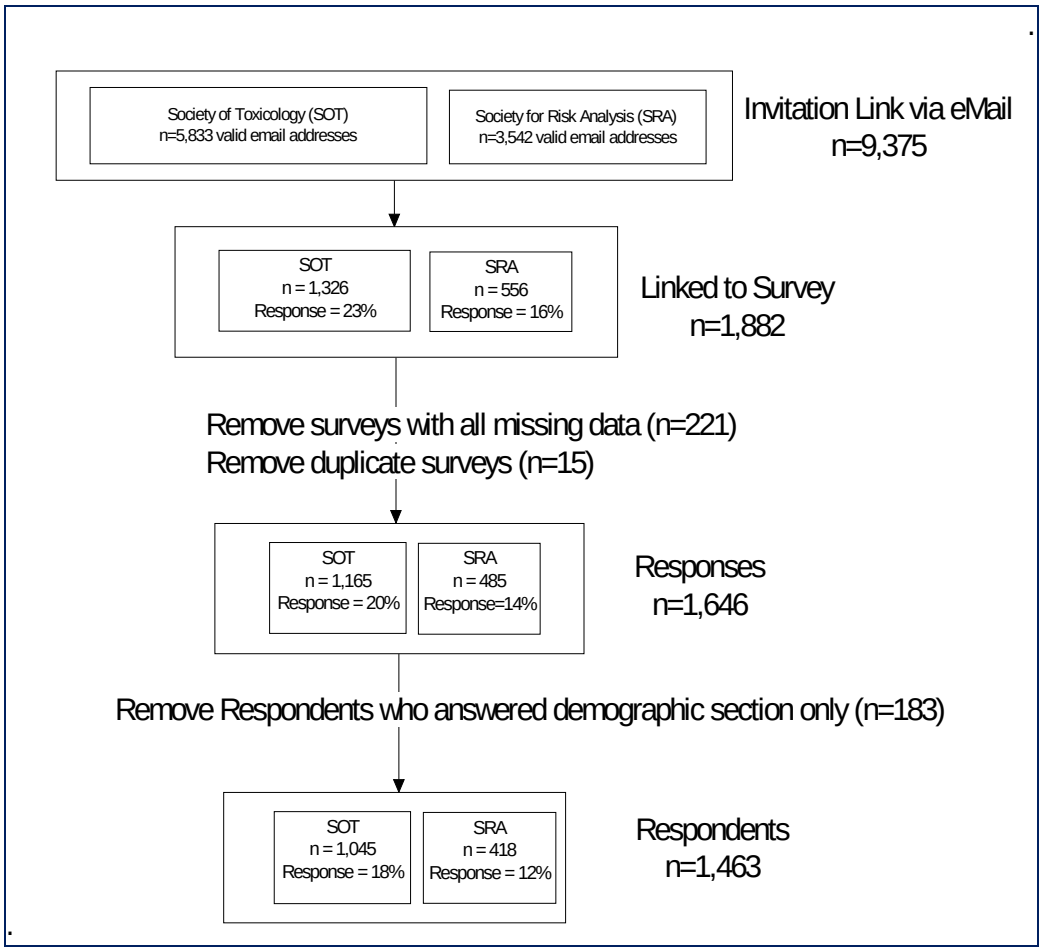

Figure 4.1: Flow diagram of overall response rate and adjusted response rate

4.2.2 Completion Rate

4.2.2.1 Completion Rate by Question

Completion rate was evaluated by question and by demographic variables of interest. Completion rate by question was calculated based on the 1,463 respondents who

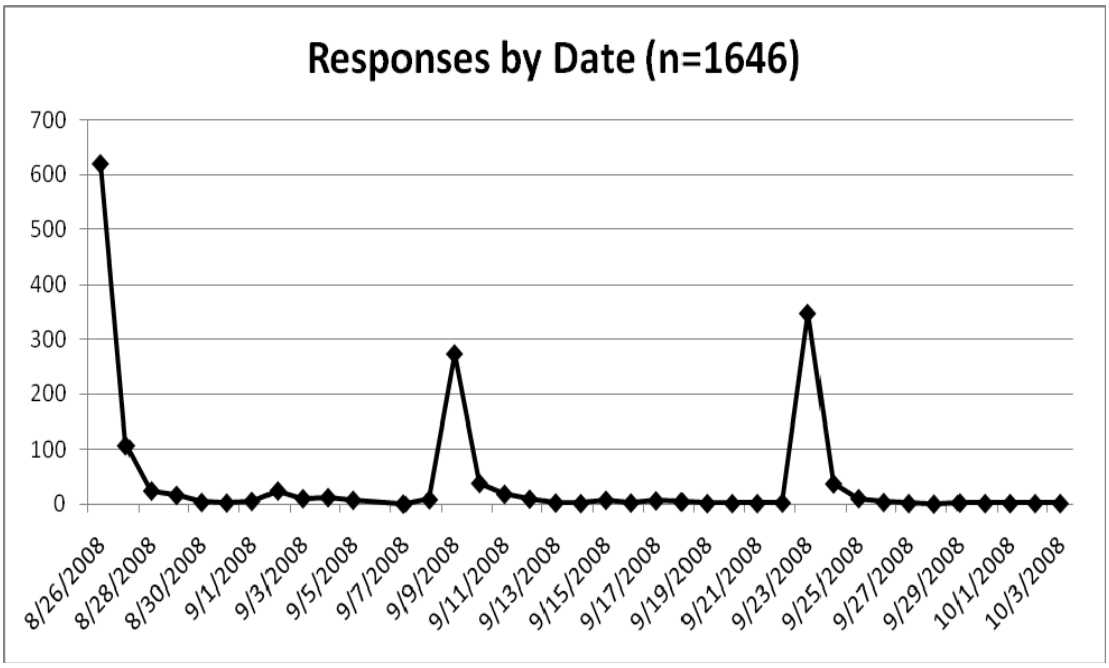

Figure 4.2: Frequency diagram of questionnaire responses by date. The spikes correspond with initial invitation 8/26 and subsequent reminder dates of 9/8 and 9/24

completed the demographic section and continued the survey through question 43. Completion rate by question, starting with question 14 is presented in Table 4.1.

4.2.2.2 Completion Rate by Demographic Variables of Interest

Completion rate was plotted by years of experience and gender. To be considered complete, the respondent must have continued the survey through question 42, 43, or 44. Experienced men tended to have a higher completion rate in most categories of years of experience than women. The only exception was for women with 10-19 years experience (Figure 4.3).

Table 4.1: Completion rate by question

Question	Responses	% Complete
14	1483	100
15	1411	95
16	1435	96
17	1437	97
18	1444	97
19	1392	94
20	1410	95
21	1410	95
22	1412	95
23	1320	89
24	1225	83
25	1442	97
26	1143	77
27	1383	93
28	1345	91
29	1196	81
30	1347	91
31	1320	89
32	1217	82
33	1315	87
34	1251	84
35	1101	74
36	1245	84
37	1291	87
38	1235	83
39	1230	83
40	1186	80
41	1239	83
42	1247	84
43	1234	83
44	1150	78

Figure 4.3: Completion rate by years of experience and gender

On average, the SOT and SRA response rates differed by society with the SOT response rate consistently higher regardless of years of experience. Response rates for both societies increased with increased years of experience (Figure 4.4).

Completion rates were examined by years of experience and by highest attained degree (Figure 4.5). The respondents with bachelor and master degrees tended to have lower completion rates, except among those with the highest years of experience.

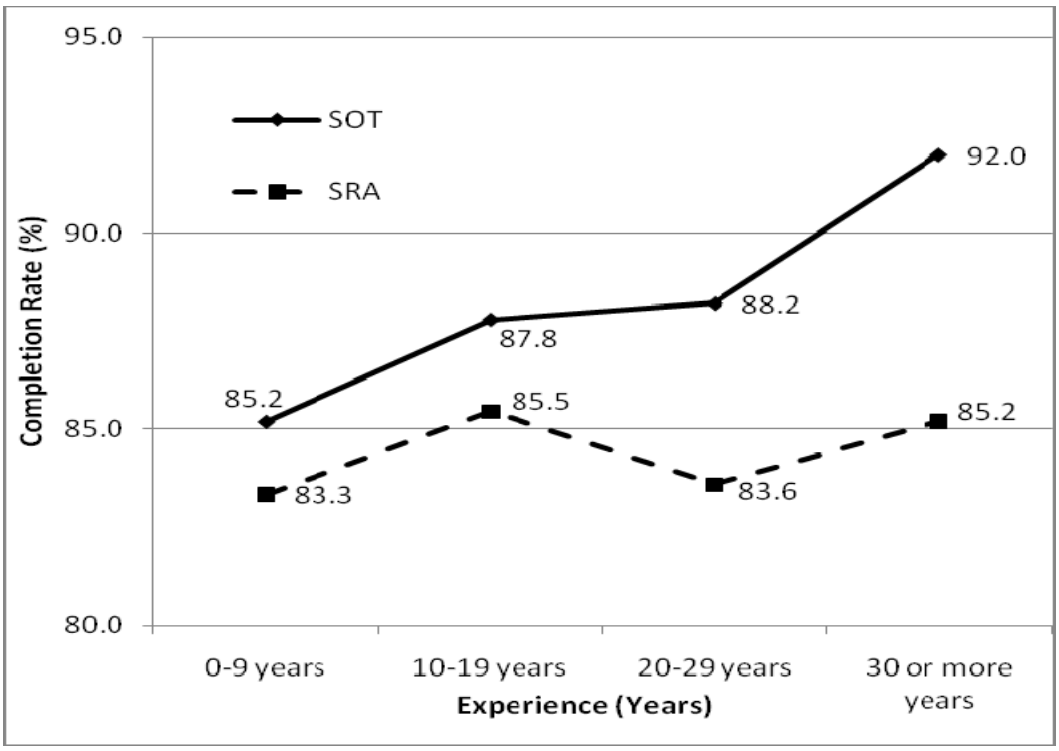

Figure 4.4: Completion rate by years of experience and society membership

Chi-square tests and multivariate regression analysis of the variables of interest (gender, society membership, highest attained degree, and years of experience) indicate subjects who completed the survey are not statistically different from those who started the survey. The only statistically significant variable was 0-9 years experience. The multivariate logistic regression analysis results are shown in Table 4.2.

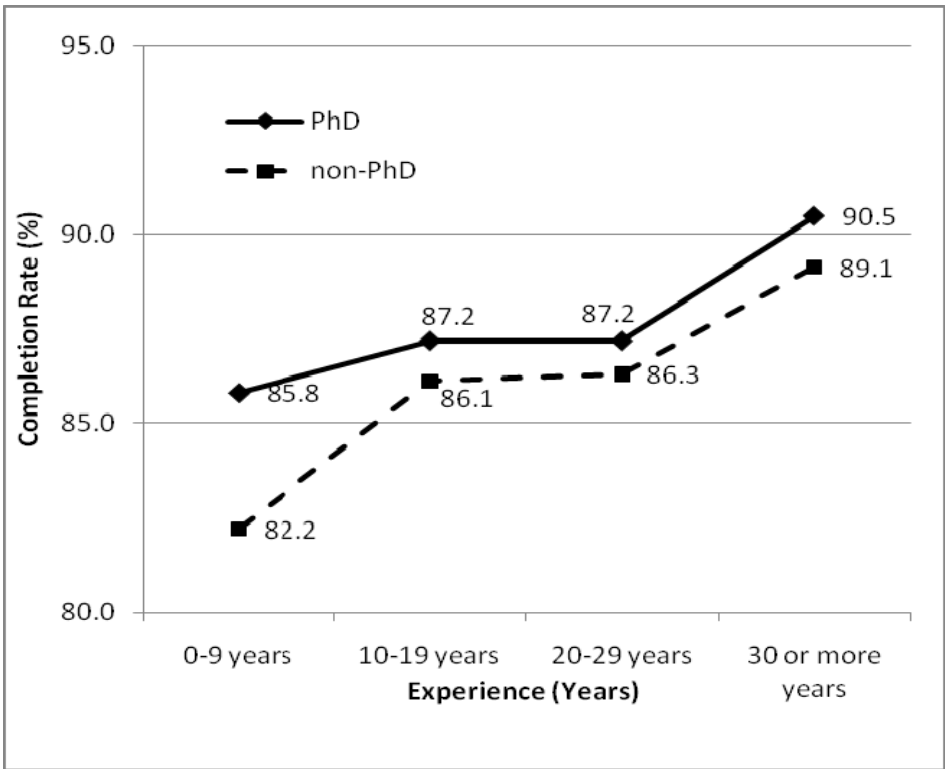

Figure 4.5: Completion rate by experience and highest degree attained

Table 4.2: Multivariate logistic regression analysis results comparing subjects who completed the survey to those who did not complete

Covariate	Completed Survey		Did not Complete		Adjusted Odds Ratio	95% CI Adjusted OR
	No.	%	No.	%		
Gender						
Male	863	88	120	12	1.00	Reference
Female	385	86	62	14	0.99	0.70, 1.40
Education						
PhD	1004	88	142	12	1.00	Reference
BS, MS, JD, MD, DVM	264	85	46	15	1.11	0.76, 1.64
Society						
SOT	921	88	124	12	1.00	Reference
SRA	352	84	66	16	0.78	0.55, 1.11
Experience						
30 or more Years	299	90	32	10	1.00	Reference
0-9 Years	351	85	63	15	0.58	0.36, 0.94
10-19 Years	274	87	41	13	0.80	0.48, 1.35
20-29 Years	344	87	53	13	0.76	0.47, 1.24

4.2.3 Respondent Characteristics

Examination of demographic variables allows for characterization of respondents. Respondent characteristics are summarized for all demographic variables, type of employment and specialty for the 1,463 people who answered the subject matter content questions of the questionnaire. Table 4.3 (top panel) provides a summary of the demographic variables by society. The table shows that among respondents gender distribution is identical between societies. The SRA respondent group had fewer PhD's but more master's degrees for highest attained degree. The frequency distributions by society for political, economic, and social views (Table 4.3 bottom panel) were for the most part remarkably similar among respondents from the different groups.

Examination by type of employment and society membership shows considerable similarity. The largest differences are seen between society members ever employed by the pharmaceutical industry and members ever employed in environmental consulting (Table 4.4).

Comparison of specialties by society shows the fundamental differences in society membership as described in Chapter 3 (Table 4.5). The SOT respondent group consists of subjects who specialize in general toxicology with a variety of toxicological sub-specialties. The SRA respondent group consists mainly of subjects with specialties in risk assessment, policy, and public health.

Table 4.3: Summary of demographic and political, economic, and social views by society

Characteristic	Society of Toxicology		Society for Risk Analysis	
	No.	%	No.	%
Gender				
Male	739	68.6	281	68.4
Female	338	31.4	130	31.6
Education				
Bachelor's	52	4.7	17	4.0
Master's	93	8.4	96	22.9
PhD	924	83.8	288	68.6
MD/JD/DVM	31	2.8	15	3.6
Experience in Years				
0-9	331	30.1	85	20.4
10-19	220	20.0	98	23.5
20-29	279	25.4	142	34.1
≥ 30	269	24.5	92	22.1
Political Issues				
Conservative	150	13.7	52	12.4
Middle of the Road	466	42.6	157	37.6
Liberal	397	36.3	176	42.1
Choose not to Respond	82	7.5	33	7.9
Economic Issues				
Conservative	278	25.4	105	25.2
Middle of the Road	558	51.1	192	46.2
Liberal	190	17.4	92	22.1
Choose not to Respond	67	6.1	27	6.5
Social Issues				
Conservative	141	12.9	47	11.3
Middle of the Road	445	40.8	120	28.8
Liberal	431	39.5	223	53.5
Choose not to Respond	75	6.9	27	6.5

Table 4.4: Summary of responses for employment area by society

Characteristic	Society of Toxicology		Society for Risk Analysis	
	No.	%[1]	No.	%[1]
Government				
NASA	.	.	3	0.7
EPA	95	8.6	56	13.3
OSHA	2	0.2	2	0.5
CDC	12	1.1	3	0.7
DOE	11	1.0	14	3.3
FDA	29	2.6	13	3.1
State	36	5.2	33	7.9
International	13	1.2	10	2.4
Other	57	5.2	30	7.1
Industry				
Pharmaceutical	225	20.4	12	2.9
General Manufacturing	34	3.1	8	1.9
Defense	5	0.5	11	2.6
Petrochemical	31	2.8	13	3.1
Chemical	90	8.2	18	4.3
Environmental Consulting	58	5.3	98	23.3
Toxicological Consult/Res.	223	20.2	71	16.9
Academic				
Administrative	27	2.5	14	3.3
Faculty	279	25.3	104	24.8
Medical Faculty	36	3.3	7	1.7
Post-Doctoral Researcher	80	7.3	16	3.8
Graduate Student	85	7.7	18	4.3
Other				
Non-governmental Org	43	3.9	24	5.7
Retired	65	5.9	28	6.7

[1] Frequencies do not add up to 100% because the respondent was able to select all employment categories that applied to their career experience

Table 4.5: Summary of responses by field of specialty

Specialty	Society of Toxicology		Society for Risk Analysis	
	No.	%[1]	No.	%[1]
General Toxicology	783	71.1	159	37.9
Risk Assessment	411	37.3	361	86.0
Regulatory Policy	174	15.8	151	36.0
Mechanistic	275	25.0	36	8.6
Carcinogenesis	230	20.9	62	14.8
Pharmacology	214	19.4	16	3.8
Public Health	144	13.1	144	34.3
Molecular	202	18.3	20	4.8
Developmental/Reproductive	196	17.8	23	5.5
Occupational	112	10.2	65	15.5
Inhalation/Respiratory	151	13.7	45	10.7
Neurotoxicology	156	14.2	22	5.2
Immunotoxicology	120	10.9	9	2.1
Biological Modeling	77	7.0	55	13.1
Pathology	78	7.1	9	2.1
Dermal	49	4.4	13	3.1
Veterinary	49	4.4	8	1.9
Ecology	33	3.0	40	9.5
Food Safety	100	9.1	47	11.2

[1] Frequencies do not add up to 100% because the respondent was able to select all employment categories that applied to their career experience.

4.2.4 Summary Statistics by Question

Summary statistics for Section 3: Knowledge and Attitudes about Interpreting Dose-Response Assessments; Section 4: Knowledge and Attitudes about the Hormesis Dose-Response; and Section 5: Knowledge and Attitudes about Risk Assessment Principles and Practice were calculated based on responses from the 1,463 subjects who continued the questionnaire after completing the demographic section. In all cases the summary statistics were calculated for responses only and do not include missing values.

4.2.4.1 Knowledge and Opinions about Interpreting Dose-Response Assessments

Section 3 contained thirteen knowledge and opinion questions meant to ascertain respondent attitudes about interpreting dose-response assessments. The first of the thirteen questions was a basic statement that dose-response assessment is the necessary foundation for risk assessment. The statement was met with virtually unanimous agreement (98%). The respondents generally disagreed (75%) with the current approach used by regulatory agencies to assess cancer risks. Respondents were closely split as to whether exposure to genotoxic carcinogens (57% agree vs. 43% disagree) or ionizing radiation (52% agree vs. 48% disagree) always leads to increased risk of developing of cancer regardless of how low the dose. Respondents disagreed for the most part (80%) that non-genotoxic carcinogens always lead to increased risk of cancer regardless of how low the dose. The section contained three questions about definitions of the threshold, linear non-threshold, and hormesis dose-response models. Respondents generally agreed (> 80%) with each definition provided. Most respondents (69%) think non-carcinogenic toxicants act in a manner consistent with the threshold dose-response model and over half (53%) think carcinogenic compounds follow the threshold model. At the end of the section respondents were asked to report their first-hand experience with various dose-response models. The threshold dose-response was reported to be observed commonly and occasionally (n=1019), followed by linear-non-threshold (n=629) then hormesis (n=555). Many who conduct dose-response research (n=233) commented that most studies are not designed to detect hormesis. The summary results for this section are found in Table 4.6.

Table 4.6: Summary statistics for Section 3 "Knowledge and Attitudes about Interpreting Dose-Response Assessments."

Question	Responses			
Q14. Dose-response assessment is a necessary foundation for understanding risk assessment.	Agree 98% (1457)		Disagree 2% (26)	
Q15. Regulatory upper-bound characterizations used in cancer risk assessments provide accurate estimates of the probability of developing cancer at low doses.	Generally Agree 25% (358)		Generally Disagree 75% (1053)	
Q16. Exposure to a genotoxic carcinogen, no matter how small, theoretically results in an increased cancer risk.	Generally Agree 57% (827)		Generally Disagree 43% (608)	
Q17. Exposure to a non-genotoxic carcinogen, no matter how small, theoretically results in an increased cancer risk.	Generally Agree 20% (285)		Generally Disagree 80% (1152)	
Q 18. Exposure to ionizing radiation (e.g. x-rays), no matter how small, theoretically results in increased cancer risk.	Generally Agree 52% (745)		Generally Disagree 48% (699)	
Q19. The linear model employed in cancer risk assessment overstates risk in the low dose zone.	Generally Agree 83% (1157)		Generally Disagree 17% (285)	
Q20. The threshold dose-response assumes no treatment related responses occur below the estimated threshold.	Generally Agree 80% (1122)		Generally Disagree 20% (288)	
Q21. The linear non-threshold (LNT) dose-response assumes a biological response is directly proportional to dose in the low dose zone.	Generally Agree 88% (1247)		Generally Disagree 12% (163)	
Q22. The hormesis dose-response exhibits biological responses at low doses that are opposite to those observed at higher doses, leading to either a J-shaped or inverted U-shaped dose-response curve.	Generally Agree 93% (1318)		Generally Disagree 7% (94)	
Q23. For effects other than carcinogenesis, most toxicants act in a manner consistent with the following model:	Threshold 69% (907)	LNT 14% (188)	Hormetic 17% (225)	
Q24. Carcinogens typically act via the following dose-response model:	Threshold 53% (649)	LNT 34% (414)	Hormetic 13% (162)	
Q25. Have you ever conducted experimental research in dose-response?	Yes 65% (946)		No 35% (496)	
Q26 a. In my research biological responses that best fit the threshold model are observed:	Commonly 68% (759)	Occasionally 23% (260)	Rarely 6% (63)	Never 3% (39)
Q26 b. In my research biological responses that best fit the linear non-threshold model are observed:	Commonly 22% (237)	Occasionally 36% (392)	Rarely 28% (309)	Never 14% (153)
Q26 c. In my research biological responses that best fit the hormesis model are observed:	Commonly 12% (127)	Occasionally 39% (428)	Rarely 33% (366)	Never 16% (171)

4.2.4.2 Knowledge and Opinions about Interpreting the Hormesis Dose-Response

Section 4 contained seven questions about the subject's knowledge and attitudes regarding hormesis dose-response. The first question was a query to ascertain how many respondents learned of hormesis in person by attending a seminar, workshop, conference or classroom instruction. Most respondents had no experience with any type of personal instruction on the topic. The second question asked about how commonly the respondent thought hormesis is reproducibly observed in a variety of study types. Most respondents either thought hormesis occurred 5-20% of the time (approximately 25% of respondents) or selected "do not know" (approximately 35% of respondents). Of the respondents who selected "do not know" 60% thought hormesis had not been adequately studied. The remaining questions in the section addressed the interpretation of dose-response models. A large majority (86%) thought biological responses to toxicant and radiation exposure were not necessarily adverse. A majority (64%) also thought the J-shaped dose response could implicate beneficial effects at low doses. Question 32, the first of four policy questions made the statement that sufficient data exist to suggest hormesis occurs in a wide range of species and endpoints following low-dose exposure to a broad range of chemical agents and physical stressors. Respondents were evenly divided on the topic. This question is analyzed in detail later in this chapter in the section on univariate and joint analysis. The last question of the section asked about the interpretation of the hormesis dose-response. A majority (71%) thought that the phenomenon of hormesis was either beneficial or harmful, depending on the biological response. The responses to all questions in this section are summarized in Table 4.7.

Table 4.7: Summary statistics for Section 4 "Knowledge and Attitudes about the Hormesis Dose-Response"

Question	Responses					
Q27 a. Have you ever attended a hormesis seminar?	Yes 34% (461)			No 66% (904)		
Q27 b. Have you ever attended a hormesis workshop?	Yes 10% (126)			No 90% (1201)		
Q27 c. Have you ever attended a hormesis conference?	Yes 7% (92)			No 93% (1241)		
Q27 d. Have you ever attended classroom instruction on hormesis?	Yes 25% (327)			No 75% (998)		
Q28 a. How commonly do you think hormesis is reproducible observed in chemical toxicity studies?	(>60%) 4% (60)	(20-60%) 21% (277)	(5-20%) 29% (388)	(1-5%) 18% (239)	(~0%) 3%(47)	Don't Know 25% (330)
Q28 b. How commonly do you think hormesis is reproducible observed in chemical carcinogen studies?	(>60%) 2% (28)	(20-60%) 13% (176)	(5-20%) 26% (345)	(1-5%) 23% (303)	(~0%) 5% (67)	Don't Know 31% (418)
Q28 c. How commonly do you think hormesis is reproducible observed in ionizing radiation studies?	(>60%) 4% (54)	(20-60%) 19% (254)	(5-20%) 21% (277)	(1-5%) 16% (215)	(~0%) 5% (67)	Don't Know 35% (467)
Q28 d. How commonly do you think hormesis is reproducible observed in human epidemiology studies?	(>60%) 3% (36)	(20-60%) 14% (188)	(5-20%) 22% (290)	(1-5%) 17% (230)	(~0%) 6% (87)	Don't Know 38% (500)
Q29. If you answered (5-20%),(1-5%), (~0%), or do not know, to the preceding question is it because you believe hormesis :	Does not occur 2% (21)	Not adequately studied 60% (715)		Is an exception 20% (240)	Not apply 18% (220)	
Q30. Any reproducible biological response to a toxic chemical or radiation exposure qualifies as an "adverse effect."	Agree 14% (188)			Disagree 86% (1159)		
Q31. If a study reliably shows a J-shaped dose-response curve, it implies low dose effects could be beneficial.	Agree 64% (843)			Disagree 36% (477)		
Q32. Sufficient data exist to suggest hormesis occurs in a wide range of species and endpoints following low-dose exposure to a broad range of chemical agents and physical stressors.	Generally Agree 48% (584)			Generally Disagree 52% (633)		
Q33. If a study reproducibly demonstrates the hormesis dose-response, the implication for low doses would be the effects are:	Likely Harmful 2% (20)	Beneficial or Harmful 71% (937)		Likely Beneficial 15% (203)	Not Likely to be Significant 12% (155)	

4.2.4.3 Knowledge and Opinions about Risk Assessment Principles and Practice

Section 5 consisted of eleven questions on risk assessment principles and practice. This section contained three policy questions. The policy questions are examined first, followed by the results of the remaining principles and practice questions.

Question 36 presented the statement "risk assessment procedures should be modified to obtain potential benefits associated with hormesis." The questions was also selected for detailed comment analysis because it was thought this question might elicit the most "passionate" response from subjects. The comments are summarized in a later section of this Chapter. A majority (68%) agreed that risk assessment procedures should be modified to identify potential benefit. Question 38 was the third policy question and it probed whether respondents would be willing to re-evaluate current regulations if the hormesis dose-response was accepted as the default model for risk assessment. Seventy-seven percent of respondents agreed that if hormesis were accepted as the default model for risk assessment, regulations should be re- evaluated. The last policy question, number 39, stated "the phenomenon of hormesis justifies a change in hazard assessment protocols (e.g. sample size, number of doses, timing of doses). A 65% majority agreed with this statement. Further analyses of all the policy questions are presented in the univariate and multivariate analysis of policy questions presented later in this chapter.

Although important in gaining an overall understanding of study respondent knowledge and attitudes about risk assessment principles and practice, the remaining questions did not undergo detailed analysis and are summarized in this section and discussed in Chapter 5. Questions 34 and 35 asked about respondent attitudes toward

chemical and ionizing radiation regulations. A majority (56%) thought current chemical regulations were reasonable and a larger majority (78%) thought ionizing radiation regulations were reasonable. In response to question 37, most (88%) thought hormesis should be subjected to the traditional use of safety factors. The remaining questions covered a variety of risk assessment topics. The responses to question 42 indicated 71% think hormesis would not reduce the need for uncertainty factors. Responses to questions 40, 41, 43, and 44 indicate that most respondents generally agree that hormesis could have a practical use in the conduct of risk assessment. The responses to all questions in this section are summarized in Table 4.8.

4.3 Tests for Association

Chi-square tests, odds ratios, and multivariate logistic regression modeling were used to identify characteristics of those who would accept or reject hormesis and to predict those who would use hormesis in the conduct of risk assessments. This section provides an examination of the four questions that were singled out for detailed analysis (questions 32, 36, 38 and 39). The selection criteria for each question are discussed in Chapter 3: Methods. This section starts with an explanation of how variables were selected for univariate analysis and then details the univariate and multivariate analysis results for each question.

Table 4.8: Summary statistics for Section 5 "Knowledge and Attitudes about Risk Assessment Principles and Practice"

Question	Responses		
Q34. What is your perspective on the current state of chemical regulation?	Too Stringent 19% (239)	Reasonable 56% (698)	Not stringent enough 25% (314)
Q35. What is your perspective on the current state of ionizing radiation regulations?	Too Stringent 13% (143)	Reasonable 78% (855)	Not stringent enough 9% (103)
Q36. Risk assessment procedures should be modified to obtain potential benefits associated with hormesis.	Generally Agree 59% (728)	Generally Disagree 41% (517)	
Q37. If a chemical exhibits a hormesis dose-response, the risk assessment should accommodate the data.	Generally Agree 88% (1128)	Generally Disagree 12% (163)	
Q38. If hormesis were accepted as the default model for risk assessment, current regulations should be re-evaluated.	Generally Agree 77% (950)	Generally Disagree 23% (285)	
Q39. The phenomenon of hormesis justifies a change in hazard assessment protocols (e.g. sample size, number of doses, timing of doses).	Agree 65% (797)	Disagree 35% (433)	
Q40. Acceptance of hormesis decreases the margin of safety in risk assessments.	Generally Agree 29% (346)	Generally Disagree 71% (840)	
Q41. The J-shaped hormetic model shown in the figure indicates that at low doses risk of disease is reduced.	Agree 62% (772)	Disagree 38% (467)	
Q42. If hormesis is present, the traditional use of safety factors or uncertainty factors is not necessary.	Generally Agree 12% (152)	Generally Disagree 88% (1095)	
Q43. If hormesis were accepted as the default model for risk assessment, current and past risk assessment decisions should be formally re-evaluated.	Generally Agree 64% (786)	Generally Disagree 36% (448)	
Q44. Risk assessments based on the hormesis dose response could address chemical mixtures as effectively as linear and threshold based risk assessments.	Generally Agree 58% (663)	Generally Disagree 42% (487)	

4.3.1 Selection of Variables for Univariate and Multivariate Analysis

The chi-square test was calculated for all variables and all questions as described in Chapter 3. The test results were exported to an Excel spreadsheet. This spreadsheet was visually scanned to identify variables that consistently demonstrated heterogeneity across multiple questions. Sixteen variables were identified as variables of interest based on the chi-square screening analysis.

The demographic variables found to be statistically significant across most questions were gender, highest attained degree, and society membership. An *a priori* hypothesis that political, economic and social views would be predictive of those who would accept or reject hormesis was not supported by the data. The variables representing years of experience, subject age, nationality, and when a subject completed the survey were not found to be potential indicators of acceptance or rejection of hormesis.

Three broad employment categories were consistently significant: 1) employment by a government regulatory agency, 2) employment in the private sector (industry) and 3) employment in academia. The category government regulatory agency contained the US Environmental Protection Agency (EPA) subset that was evaluated and consistently found to be predictive of a lower acceptance rate, but not a rejection of hormesis as will be explained later in this chapter. Three US government agencies showed a strong acceptance of hormesis based on chi-square screening, Department of Energy, Department of Defense, and the Food and Drug Administration but were not were not carried forward as variables for detailed examination due to the low total number of

subjects in each category (n<100). Subjects who worked for State government agencies had a low acceptance rate for hormesis but were not carried forward, also due to low numbers (n< 100). The industry category contained two employment subsets that were significant and proved predictive of opinions toward hormesis; ever employed by the pharmaceutical industry and ever employed in environmental consulting. The remaining variables representing industry classifications were not significant. Note that respondents could select multiple job categories. Most respondents selected one job category (n=1,088). The remaining subjects selected none (n=27), two categories (n=201) or three or more categories (n=147).

The specialty variables found to be statistically significant and with a sufficient number of respondents (n>100) to carry forward in the analysis were general toxicology, developmental and reproductive toxicology, inhalation toxicology, neurotoxicology, regulatory policy, and risk assessment. The veterinary and ecology specialties were consistently accepting of hormesis, but were not carried forward due to low numbers of respondents (n<100). As with job categories, respondents were asked to select all specialty categories that applied. Most subjects selected two categories (n=321), followed closely by those that selected one category (n=315). Many respondents selected three (n=288) and four (n=230) specialty categories.

Univariate odds ratios were calculated for each variable. Variables found to be statistically significant were entered as covariates into the multivariate logistic regression analysis.

4.3.2 Univariate and Multivariate Analysis of Policy Questions

4.3.2.1 Univariate and Multivariate Analysis of Policy Question 32 About the Widespread Applicability of the Hormesis Dose-Response Model

Question 32 specifically states "sufficient data exist to suggest hormesis occurs in a wide range of species and endpoints following low-dose exposure to a broad range of chemical agents and physical stressors." The overall result was that 48% of respondents agreed with the statement. The sixteen variables of interest were examined and the results are shown in Table 4.9. Only two variables, women (OR=0.75, 95% CI=0.58, 0.96) and pharmaceutical industry employment (OR=0.59, 95% CI=0.42, 0.83) were found to be significantly associated with the view of the widespread applicability of the hormesis dose-response model, both in the direction of not subscribing to this view of hormesis.

The two variables were entered as covariates in the logistic regression analysis shown in Table 4.10. Both remained significantly associated after adjustment. Therefore, the null hypotheses of no difference between male and female respondents, and no difference between pharmaceutical workers and all other workers were rejected. Women and respondents who were ever employed by the pharmaceutical industry are more likely to disagree with question 32, that hormesis is common across species and endpoints.

Table 4.9: Univariate analysis results for question 32 on the universality of the hormesis dose-response

Variable	Agree		Disagree		Odds Ratio	95% CI[1]	*P*-Value
	No.	%	No.	%			
Gender							
Male	410	51	306	49	1.0	Reference	-
Female	158	43	206	57	0.75	0.58, 0.96	0.024
Education							
BS/MS	114	48	124	52	1.0	Reference	-
PhD, JD,MD,DVM	459	48	495	52	1.0	0.75, 1.35	1.0
Society							
SOT	413	47	460	53	1.0	Reference	-
SRA	162	50	162	50	1.14	0.86, 1.44	0.445
Gov't Reg. Agency							
No	467	49	494	51	1.0	Reference	-
Yes	108	46	128	54	0.89	0.66, 1.20	.479
EPA Only							
No	552	48	589	52	1.0	Reference	-
Yes	23	41	33	59	0.75	0.41, 1.32	0.351
Ever EPA							
No	532	47	561	52	1.0	Reference	-
Yes	43	41	61	59	0.74	0.48, 1.14	0.184
Ever Industry							
No	291	49	301	51	1.0	Reference	-
Yes	284	47	321	53	0.91	0.72, 1.16	0.479
Ever Pharmaceutical							
No	506	50	506	50	1.0	Reference	-
Yes	69	37	116	63	0.59	0.42, 0.83	0.001
Ever Envron. Consult							
No	507	47	566	53	1.0	Reference	-
Yes	68	55	56	45	1.36	0.93, 2.01	0.132
Academic							
No	398	47	456	53	1.0	Reference	-
Yes	177	52	116	48	1.22	0.94, 1.58	0.133
General Toxicology							
No	233	50	231	50	1.0	Reference	-
Yes	342	47	391	53	0.87	0.68, 1.10	0.254
Devel/Reproductive							
No	491	48	535	52	1.0	Reference	-
Yes	84	49	87	51	1.05	0.75, 1.47	0.822
Inhalation Toxicology							
No	508	48	543	34	1.0	Reference	-
Yes	67	56	79	35	0.91	0.63,1.30	0.642
Neurotoxicology							
No	508	48	554	52	1.0	Reference	-
Yes	67	50	68	50	1.07	0.76, 1.56	0.762
Regulatory Policy							
No	471	49	488	35	1.0	Reference	-
Yes	104	44	134	37	0.80	0.59, 1.08	0.154
Risk Assessment							
No	299	48	323	33	1.0	Reference	-
Yes	276	48	299	37	1.0	0.78, 1.25	1.0

Abbreviations: CI, Confidence Interval; Gov't Reg. Agency, government regulatory agency; Envron, environmental; Devel, developmental

Table 4.10: Multivariate logistic regression analysis results for question 32 on the widespread applicability of the hormesis dose-response model

Covariate	Agree		Disagree		Univariate Odds Ratio	Adjusted Odds Ratio	95% CI[1] Adjusted OR
	No.	%	No.	%			
Gender							
Male	410	51	306	49	1.0	1.0	Reference
Female	158	43	206	57	0.75	0.72	0.56, 0.93
Ever Pharmaceutical							
No	506	50	506	50	1.0	1.0	Reference
Yes	69	37	116	63	0.59	0.58	0.42, 0.80

Abbreviations: CI, confidence interval; OR, odds ratio

4.3.2.2 Univariate and Multivariate Analysis of Policy Question 36 about Modifying Risk Assessment Procedures to Include Potential Benefit

Question 36 specifically states "Risk assessment procedures should be modified to obtain potential benefits associated with hormesis." This question was designed to evaluate whether respondents would accept modifying risk assessment procedures to include potential benefit associated with hormesis. The overall result for this question was 59% agreed procedures should be modified to include potential benefit. Additional analysis was conducted to ascertain which respondents were most likely to agree. The sixteen variable of interest were examined and the results are shown in Table 4.11. The odds ratios and 95% CI indicated the following eight variables could be predictive of acceptance or rejection: 1) highest degree attained; 2) employment by a government regulatory agency; 3) being employed only by EPA; 4) being ever employed by EPA; 5) employment in the private sector (industry); 6) employment as an environmental

Table 4.11: Univariate analysis for question 36 about modifying risk assessment procedures to obtain benefit from hormesis

Variable	Agree		Disagree		Odds Ratio	95% CI[1]	*P*-Value
	No.	%	No.	%			
Gender							
Male	490	59	341	41	1.0	Reference	-
Female	213	59	150	41	0.99	0.76, 1.28	0.976
Education							
BS/MS	167	66	86	34	1.0	Reference	-
PhD, JD,MD,DVM	543	57	417	43	0.67	0.49, 0.90	0.008
Society							
SOT	505	58	370	43	1.0	Reference	-
SRA	209	61	134	39	1.14	0.88, 1.43	0.336
Gov't Reg. Agency							
No	597	61	381	39	1.0	Reference	-
Yes	117	49	123	51	0.61	0.45, 0.81	0.0007
EPA Only							
No	695	60	464	40	1.0	Reference	-
Yes	19	32	40	68	0.32	0.17, 0.57	<0.0001
Ever EPA							
No	666	60	442	40	1.0	Reference	-
Yes	48	44	62	56	0.51	0.34, 0.78	0.001
Ever Industry							
No	341	56	273	44	1.0	Reference	-
Yes	373	62	231	38	1.29	1.03, 1.64	0.032
Ever Pharmaceutical							
No	605	58	430	42	1.0	Reference	-
Yes	109	60	74	40	1.04	0.75, 1.46	0.844
Ever Envron. Consult							
No	629	58	463	42	1.0	Reference	-
Yes	85	67	41	33	1.56	1.02, 2.32	0.04
Academic							
No	499	58	359	42	1.0	Reference	-
Yes	215	60	145	40	1.07	0.82, 1.38	0.659
General Toxicology							
No	299	61	192	39	1.0	Reference	-
Yes	418	57	312	43	0.85	0.67, 1.29	0.20
Devel/Reproductive							
No	627	60	421	40	1.0	Reference	-
Yes	87	51	83	49	0.70	0.50, 0.99	0.04
Inhalation Toxicology							
No	636	59	435	41	1.0	Reference	-
Yes	78	53	69	47	0.78	0.55, 1.12	0.171
Neurotoxicology							
No	649	60	431	40	1.0	Reference	-
Yes	65	47	73	53	0.59	0.41, 0.86	0.005
Regulatory Policy							
No	568	58	409	42	1.0	Reference	-
Yes	146	61	95	39	1.11	0.82, 1.49	0.154
Risk Assessment							
No	367	58	264	42	1.0	Reference	-
Yes	347	59	240	41	1.04	0.82, 1.31	0.780

Abbreviations: CI, Confidence Interval; Gov't Reg. Agency, government regulatory agency; Envron, environmental; Devel, developmental

consultant; 7) specializing in developmental and reproductive toxicology; and 8) specializing in neurotoxicology.

The variables representing employment in government regulatory agency, EPA only, and Ever EPA were found to be highly correlated. The variable "Gov't Reg. Agency" was selected to carry forward in the multivariate logistic regression model because the 95% CI was smaller and the total number of respondents was larger. The variables ever employed industry and ever employed environmental consultant also found to be statistically correlated. Ever employed industry was selected for the multivariate logistic regression model because it had the narrowest 95% CI and the largest number of respondents. In addition to the sixteen variables of interest, political, social and economic views were identified by chi-square screening analysis to be statistically significant for question 36. Univariate and multivariate analysis of political, social and economic views was conducted to determine whether the variables were correlated, and if so, select the variable that would be entered into the multivariate logistic regression model. For this analysis the reference group was set as "conservative". Based on the results of the analysis the variable "political" had the most significant odds ratios (i.e., lowest significance level) after adjusting for the effects of the covariates social and economic; thus was selected for the overall multivariate analysis of question 36. The univariate and multivariate analysis of the covariates (political, social, and economic) are summarized in Table 4.12.

Six variables were entered into the multivariate analysis. Four variables remained significant when adjusted for the effects of the other covariates. The adjusted odds ratios resulting from the multivariate logistic regression analysis are shown in table 4.13.

Table 4.12: Univariate and multivariate analysis for political, social, and economic variables for question 36 about modifying risk assessment procedures to obtain benefit from hormesis

Variable	Agree		Disagree		Odds Ratio	95% CI Univariate	Adjusted Odds Ratio	95% CI Adjusted
	No.	%	No.	%				
Political								
Conservative	108	67	54	33	1.0	Reference	1.0	Reference
Middle of the	315	62	192	38	0.82	0.56, 1.19	0.66	0.39, 1.12
Road	243	53	215	47	0.56	0.39, 0.82	0.58	0.32, 1.06
Liberal	45	54	39	46	0.58	0.34, 0.98	0.70	0.27, 1.75
Choose no Response								
Social	94	61	59	39	1.0	Reference	1.0	Reference
Conservative	295	65	160	35	1.15	0.79, 1.69	0.66	0.98, 2.76
Middle of the	280	54	243	46	0.72	0.50, 1.04	0.58	0.67, 1.95
Road	40	53	36	47	0.70	0.40, 1.21	0.70	0.37, 3.76
Liberal								
Choose no Response								
Economic								
Conservative	195	64	109	36	1.0	Reference	1.0	Reference
Middle of the	349	59	245	41	0.79	0.60, 1.06	0.88	0.63, 1.24
Road	126	53	111	47	0.63	0.49, 0.90	0.87	0.56, 1.36
Liberal	37	51	36	49	0.57	0.34, 0.96	0.69	0.23, 2.12
Choose no Response								

Table 4.13: Multivariate logistic regression analysis results for question 36 about modifying risk assessment procedures to include benefit from hormesis

Covariate	Agree		Disagree		Univariate Odds Ratio	Adjusted Odds Ratio	95% CI Adjusted OR
	No.	%	No.	%			
Education							
BS/MS	167	66	86	34	1.0	1.0	Reference
PhD, MD, JD, DVM	543	57	417	43	0.67	0.68	0.51. 0.92
Gov't Reg. Agency							
No	597	61	381	39	1.0	1.0	Reference
Yes	117	49	123	51	0.61	0.63	0.47, 0.85
Ever Industry							
No	341	56	273	44	1.0	1.0	Reference
Yes	373	62	231	38	1.29	1.09	0.86, 1.40
Develop/Reproductive							
No	627	60	421	40	1.0	1.0	Reference
Yes	87	51	83	49	0.70	0.80	0.57, 1.12
Neurotoxicology							
No	649	60	431	40	1.0	1.0	Reference
Yes	65	47	73	53	0.59	0.67	0.46, 0.97
Political							
Conservative	108	67	54	33	1.0	1.0	Reference
Middle of the Road	315	62	192	38	0.82	0.83	0.57, 1.21
Liberal	243	53	215	47	0.56	0.58	0.40, 0.85
Choose no Response	45	54	39	46	0.58	0.55	0.32, 0.96

Abbreviations: Gov't Reg Agency, Government Regulatory Agency; OR, odds ratio

Respondents with the highest attained degree of PhD were in overall agreement with modifying risk assessment to accommodate hormesis (57%) but were significantly less likely to agree than respondents with bachelor and masters degrees (66%).

Respondents ever employed by a government regulatory agency were less likely to accept a change to accommodate hormesis (49% agree). Employment by industry was not a significant indicator when adjusted for the effects of the other covariates.

The specialty of developmental and reproductive toxicology was not a significant predictor in the model. However, the specialty of neurotoxicology remained significant

and subjects with this specialty were less likely to agree with changing risk assessment procedures to evaluate potential benefit (47% agree).

Compared to political conservatives; respondents who had liberal views or chose not to respond, were less likely to agree that risk assessment procedures should be modified to obtain potential benefits associated with hormesis.

Question 36 was selected for detailed comment analysis because it was thought that this question might elicit a "passionate" response about the respondent's opinion of hormesis. The question received 323 comments. Only questions, 16, 24, and 30 received more comments. The comments were scored, positive, negative and neutral/explanation of response. One comment was scored as positive, 23 responses were negative, remaining responses were scored as neutral because the respondent was simply explaining his/her choice for agreeing or disagreeing or providing suggestions for improving clarity and meaning of the question. Negative comments tended to focus on two themes; perceived dangers in including an analysis of benefit and creation of an "industry loophole." Neutral comments were directed to the need for conclusive data supporting benefit. If the respondent agreed with question 36, the comment indicated more data were needed. If the respondent disagreed, the comment was a caveat that agreement depended on sufficient conclusive data. The implications of the comments are explored further in Chapter 5: Discussion.

4.3.2.3 Univariate and Multivariate Analysis of Policy Question 38 about Re-Evaluating Regulations if Hormesis Were the Default Model

The question specifically states "If hormesis were accepted as the default model for risk assessment, current regulations should be re-evaluated." Many of the current government regulations are based on default dose-response models; linear-non threshold for carcinogenic compounds and threshold for all other potential toxicants. This question requests the respondent to consider a situation in which the regulatory default was the hormesis dose-response and asks whether regulations should be re-evaluated. The overall result for this question was that 77% of respondents agreed regulations should be re-evaluated.

Four variables met the criteria for statistical significance: 1) highest attained degree 2) ever employed by a government regulatory agency 3) employed only by EPA and 4) ever employed by EPA. The variables representing employment in government regulatory agency, EPA only, and Ever EPA were found to be highly correlated. The variable "Gov't Reg. Agency" was selected to carry forward in the multivariate logistic regression model because the 95% CI was narrower in the univariate analysis and the total number of respondents was larger. Results of the univariate analysis on the variables of interest are presented in Table 4.14.

Highest attained degree and ever employed by a government regulatory agency, were entered as covariates in a logistic regression analysis. The two covariates remained significant when adjusted for the effects of one another. Although 76% of respondents with PhD's agreed that current regulations should be re-evaluated if hormesis were accepted as the default risk assessment model, they were significantly less likely to agree

Table 4.14: Univariate analysis results for question 38 about re-evaluating regulations if hormesis were the default model

Variable	Agree		Disagree		Odds Ratio	95% CI	*P*-Value
	No.	%	No.	%			
Gender							
Male	636	77	193	23	1.0	Reference	-
Female	283	79	73	21	1.18	0.86, 1.62	0.33
Education							
BS/MS	204	83	42	17	1.0	Reference	-
PhD, JD,MD,DVM	724	76	230	24	0.65	0.44, 0.94	0.021
Society							
SOT	668	76	207	24	1.0	Reference	-
SRA	265	80	65	20	1.26	0.92, 1.76	0.163
Gov't Reg. Agency							
No	769	79	200	21	1.0	Reference	-
Yes	164	69	72	31	0.59	0.43, 0.83	0.002
EPA Only							
No	901	78	249	22	1.0	Reference	-
Yes	35	58	23	42	0.42	0.24, 0.76	0.004
Ever EPA							
No	867	79	234	21	1.0	Reference	-
Yes	66	63	38	37	0.47	0.30, 0.74	0.001
Ever Industry							
No	458	76	141	24	1.0	Reference	-
Yes	475	78	131	22	1.12	0.84, 1.48	0.466
Ever Pharmaceutical							
No	799	78	223	22	1.0	Reference	-
Yes	134	73	49	27	0.76	0.53, 1.12	0.170
Ever Envron. Consult							
No	826	77	252	23	1.0	Reference	-
Yes	107	84	20	16	1.63	0.98, 2.84	0.06
Academic							
No	660	77	197	23	1.0	Reference	-
Yes	268	78	75	22	1.07	0.78, 1.46	0.735
General Toxicology							
No	384	80	95	20	1.0	Reference	-
Yes	549	76	177	24	0.77	0.57, 1.02	0.07
Devel/Reproductive							
No	805	78	228	22	1.0	Reference	-
Yes	128	74	44	26	0.82	0.56, 1.23	0.356
Inhalation Toxicology							
No	826	78	229	22	1.0	Reference	-
Yes	107	71	43	29	0.69	0.46, 1.04	0.075
Neurotoxicology							
No	832	78	240	22	1.0	Reference	-
Yes	102	76	32	24	0.91	0.59, 1.44	0.73
Regulatory Policy							
No	753	77	220	23	1.0	Reference	-
Yes	180	78	52	22	1.01	0.72, 1.45	1.0
Risk Assessment							
No	483	77	143	23	1.0	Reference	-
Yes	450	78	129	22	1.03	0.78, 1.37	0.87

Abbreviations: CI, Confidence Interval; Gov't Reg. Agency, government regulatory agency; Envron, environmental; Devel, developmental

than respondents with bachelor and masters degrees. The result for was similar for respondents ever employed by a government regulatory agency (69 vs.79%). The adjusted odds ratios are presented in Table 4.15.

Table 4.15: Multivariate logistic regression results for question 38 about re-evaluating regulations if hormesis were the default model

Covariate	Agree		Disagree		Univariate Odds Ratio	Adjusted Odds Ratio	95% CI Adjusted OR
	No.	%	No.	%			
Education							
BS/MS	204	83	42	17	1.0	1.0	Reference
PhD, JD, MD, DVM	724	76	230	24	0.65	0.64	0.44, 0.92
Gov't Reg. Agency							
No	769	79	200	21	1.0	1.0	Reference
Yes	164	69	72	31	0.59	0.59	0.43, 0.81

Abbreviations: Gov't Reg. Agency, government regulatory agency; OR, odds ratio

4.3.2.4 Univariate and Multivariate Analysis of Policy Question 39 about Modifying Hazard Assessment to Accommodate the Phenomenon of Hormesis

The question specifically states "The phenomenon of hormesis justifies a change in hazard assessment protocols (e.g. sample size, number of doses, timing of doses)."

The overall result was that 65% of respondents agreed with the statement. This is an important indicator as to whether researchers would accept changing hazard assessment design including sample size, timing and number of doses in order to reliably detect a hormetic dose-response.

Eight variables met the criteria for statistical significance: 1) being a woman; 2) employment by a government regulatory agency; 3) employment only by EPA; 4) employment in the pharmaceutical industry; 5) employment as an environmental

Table 4.16: Univariate analysis results for question 39 about modifying hazard assessment to accommodate hormesis

Variable	Agree		Disagree		Odds Ratio	95% CI	*P*-Value
	No.	%	No.	%			
Gender							
Male	518	63	306	37	1.0	Reference	-
Female	255	72	101	28	1.49	1.13, 1.98	0.004
Education							
BS/MS	175	70	76	30	1.0	Reference	-
PhD, JD,MD,DVM	603	64	342	36	0.76	0.56, 1.04	0.093
Society							
SOT	562	64	312	36	1.0	Reference	-
SRA	219	67	108	33	1.13	0.85, 1.49	0.427
Gov't Reg. Agency							
No	650	67	320	33	1.0	Reference	-
Yes	131	57	100	43	0.65	0.48, 0.87	.004
EPA Only							
No	755	60	392	34	1.0	Reference	-
Yes	26	48	28	52	0.48	0.27, 0.87	0.01
Ever EPA							
No	722	66	377	34	1.0	Reference	-
Yes	59	58	43	42	0.72	0.47, 1.11	0.141
Ever Industry							
No	395	66	200	34	1.0	Reference	-
Yes	386	64	220	36	0.89	0.70, 1.13	0.359
Ever Pharmaceutical							
No	686	67	332	33	1.0	Reference	-
Yes	95	52	88	48	0.52	0.38, 0.73	<0.0001
Ever Envron. Consult							
No	682	63	394	37	1.0	Reference	-
Yes	99	79	26	21	2.20	1.39, 3.59	0.0004
Academic							
No	537	63	318	37	1.0	Reference	-
Yes	244	71	102	29	1.42	1.07, 1.87	0.013
General Toxicology							
No	327	69	145	31	1.0	Reference	-
Yes	454	62	275	38	0.73	0.57, 0.94	0.015
Devel/Reproductive							
No	667	65	363	35	1.0	Reference	-
Yes	114	67	57	33	1.01	0.76, 1.56	0.69
Inhalation Toxicology							
No	699	66	354	34	1.0	Reference	-
Yes	82	55	66	35	0.63	0.44, 0.91	0.012
Neurotoxicology							
No	691	65	375	35	1.0	Reference	-
Yes	90	67	45	33	1.08	0.73, 1.62	0.748
Regulatory Policy							
No	633	65	334	35	1.0	Reference	-
Yes	148	63	86	37	0.91	0.67, 1.24	0.573
Risk Assessment							
No	413	67	205	33	1.0	Reference	-
Yes	368	63	215	37	0.85	0.66, 1.08	0.198

Abbreviations: CI, Confidence Interval; Gov't Reg. Agency, government regulatory agency; Envron, environmental; Devel, developmental

consultant; 6) employment in academia; 7) specializing in general toxicology; and 8) specializing inhalation toxicology. Odds ratios and 95% confidence intervals for all variables are presented in Table 4.16.

Because half the variables were statistically significant and potential indicators of who accept modifying hazard assessment to accommodate hormesis, the variables were tested for correlation using step-wise logistic regression analysis. The variable ever employed by a government regulatory agency was selected for the multivariate logistic regression over the EPA subsets because the confidence interval was narrower and the total number of respondents was larger. Correlation testing indicated the remaining variables were not correlated and all were entered into the multivariate analysis.

Seven variables were entered into the multivariate logistic regression model. Five variables remained significant after adjusting for the effects of covariates. Women were more likely than men to agree with changing hazard assessment protocols (72 vs.63%). Respondents that were ever employed as environmental consultants were more likely to agree when compared to all other employment categories (79 vs. 63%). Respondents ever employed by a government regulatory agency (57%) or ever employed by a pharmaceutical company (52%) were less likely to agree with changing hazard assessment protocols as compared to all other employment categories. Respondents with the specialty of inhalation toxicology were less likely to agree to changes in hazard assessment protocols than all other specialties (55%). The variables “ever employed in an academic setting” and “specialty general toxicology” were no longer significant when adjusted for the effects of the other covariates. The adjusted odds ratios are provided in Table 4.17.

Table 4.17: Multivariate analysis results for question 39 about modifying hazard assessment to accommodate hormesis

Covariate	Agree		Disagree		Univariate	Adjusted	95% CI
	No.	%	No.	%	Odds Ratio	Odds Ratio	Adjusted OR
Gender							
Male	518	63	306	37	1.0	1.0	Reference
Female	255	72	101	28	1.49	1.44	1.09, 1.90
Gov't Reg. Agency							
No	650	67	320	33	1.0	1.0	Reference
Yes	131	57	100	43	0.65	0.61	0.44, 0.83
Ever Pharmaceutical							
No	686	67	332	33	1.0	1.0	Reference
Yes	95	52	88	48	0.52	0.58	0.41, 0.82
Ever Envron. Consult							
No	682	63	394	37	1.0	1.0	Reference
Yes	99	79	26	21	2.20	2.11	1.32, 3.37
Inhalation							
Toxicology	699	66	354	34	1.0	1.0	Reference
No	82	55	66	35	0.63	0.64	0.45, 0.92
Yes							

Abbreviations: CI, Confidence Interval; Gov't Reg. Agency, government regulatory agency; Envron, environmental; OR, odds ratio

4.3.2.5 Evaluation of Question 26 about Respondents' Actual Observations of Hormetic Dose-Response on Response to the Four Policy Questions

Question 26 asks respondents about their dose-response research observations. The purpose of evaluating this question was to determine whether first-hand observation of a hormetic dose-response effect, affects respondents attitudes toward hormesis. Of the approximately 1,100 respondents with direct research experience observing biological responses, approximately half (n=555) reported direct experience observing a hormetic dose-response either commonly or occasionally. The results are provided in Table 4.18.

The 555 respondents who commonly or occasionally observed biological responses that best fit the hormesis dose response were evaluated to determine whether their opinions on the policy questions differed from their colleagues who rarely or never

Table 4.18: Data on respondents who reported observing biological responses that best fit the threshold, linear non-threshold, and hormetic dose-response models

Q26: In my research biological responses that best fit the following model are:	Common		Occasional		Rare		Never	
	No.	%	No.	%	No.	%	No.	%
Hormesis	127	12	428	39	366	34	171	16
LNT	237	22	392	36	309	28	153	14
Threshold	759	68	260	23	63	6	39	3

Abbreviations: LNT, linear non-threshold

observed hormesis. This group with direct experience observing a hormetic dose-response had a tendency to agree with the policy questions that favor hormesis, whereas those who had rare to no personal research experience observing a hormetic dose-response were less likely to favor hormesis, except for question 38 on hormesis as the default model. The results are provided in Table 4.19.

Table 4.19: Results for respondents who observed hormesis commonly, occasionally, rarely or never vis-a-vis the four policy questions

In my research hormesis dose response is observed:	Q32[1] General % Agree	Q36[2] Benefit % Agree	Q38[3] Default % Agree	Q39[4] Dosing % Agree
Commonly	79	75	82	81
Occasionally	58	65	81	73
Rarely	31	50	74	54
Never	31	42	65	57

1. Q32 Sufficient data exist to suggest hormesis occurs in a wide range of species and endpoints following low-dose exposure to a broad range of chemical agents and physical stressors.
2. Q36 Risk assessment procedures should be modified to obtain potential benefits associated with hormesis.
3. Q38 If hormesis were accepted as the default model for risk assessment, current regulations should be re-evaluated.
4. Q39 The phenomenon of hormesis justifies a change in hazard assessment protocols (e.g. sample size, number of doses, timing of doses).

4.4 Internal Consistency Analysis

Two tests for internal consistency were built into the questionnaire. Chronbach's coefficient alpha was used as the statistical measure of internal reliability. This statistic tests whether the survey elicits consistent and reliable responses between questions designed to ask related questions that have similar responses. The Alpha coefficient ranges between 0 and 1, with higher scores indicating greater internal consistency.

For this survey, if a person disagreed with question 15 "Regulatory upper-bound characterizations used in cancer risk assessments provide accurate estimates of the probability of developing cancer" they were thought to be likely to answer agree to question 19 "the linear model employed in cancer risk assessment overstates risk in the low dose zone" because both questions evaluate the respondents opinion on the current dose-response default model for cancer risk assessment. The result was 0.24, indicating a moderately low consistency in responses.

The second test was between questions 31 and 41. Question 31 states "if a study reliably shows a J-shaped dose response curve, it implies low dose effects could be beneficial." Question 41 makes essentially the same statement "the J-shaped hormetic model shown in the figure indicates that at low doses risk of disease is reduced." The Chronbach's alpha coefficient for this comparison was 0.51.

4.5 Evaluation of Response Bias

The purpose of this section is to address concerns that those who responded to the survey differed from those who did not. The first step of the evaluation was conducted by analyzing responses between those who completed the survey and those who did not.

Then auxiliary information provided by the SOT on membership characteristics was used to compare with SOT study respondents to identify whether large differences existed between society membership as a whole and study respondents. Additional information was provided by researchers conducting a similar survey shortly after the current survey, which was used to further examine potential for response bias. Finally, coded comments were evaluated.

4.5.1 Comparisons of Subjects who Completed the Questionnaire to Subjects who Did Not

In order to address concerns about response bias the characteristics of those who completed the survey were compared to those who started the survey, but dropped out along the way. The null hypothesis tested was that there was no difference between those who started and those who completed.

The sixteen variables evaluated for the four policy questions were also evaluated for this analysis. The only variables that were statistically significant were 1) being a member of the Society for Risk Analysis and 2) selecting "choose not to respond" as an answer to the social, economic, and political views questions. These results are discussed further in Chapter 5. Analytical results for the sixteen variables of interest plus social, economic, and political views are shown in Tables 4.20 and 4.21.

Table 4.20: Univariate analysis of sixteen variables tested for policy questions comparing respondents who completed the questionnaire (answered Q43) to respondents who dropped out in Sections 3, 4, or 5

Variable	Dropped		Completed		Odds Ratio	95% CI[1]	*P*-Value
	No.	%	No.	%			
Gender							
Male	167	17	816	83	1.0	Reference	-
Female	93	21	354	79	1.3	0.96, 1.79	0.08
Education							
BS/MS	68	22	242	78	1.0	Reference	-
PhD, JD,MD,DVM	201	18	945	82	0.75	0.56, 1.03	0.07
Society							
SOT	175	17	870	83	1.0	Reference	-
SRA	96	23	322	77	1.48	1.12, 1.96	0.005
Gov't Reg. Agency							
No	210	18	956	82	1.0	Reference	-
Yes	61	21	227	79	1.23	0.90, 1.70	.19
EPA Only							
No	254	18	1139	82	1.0	Reference	-
Yes	17	24	53	76	1.44	0.82, 2.53	0.20
Ever EPA							
No	245	18	1089	82	1.0	Reference	-
Yes	26	20	103	80	1.12	0.71, 1.76	0.62
Ever Industry							
No	142	19	589	81	1.0	Reference	-
Yes	129	18	603	82	1.29	0.91, 1.81	0.10
Ever Pharmaceutical							
No	220	18	1010	82	1.0	Reference	-
Yes	51	22	182	78	1.29	0.91, 1.81	0.37
Ever Envron. Consult							
No	251	19	1065	81	1.0	Reference	-
Yes	20	14	127	86	0.67	0.41, 1.10	0.11
Academic							
No	199	19	855	81	1.0	Reference	-
Yes	72	18	337	82	0.92	0.68, 1.23	0.57
General Toxicology							
No	115	19	478	81	1.0	Reference	-
Yes	156	18	714	82	0.91	0.69, 1.19	0.48
Devel/Reproductive							
No	239	19	1019	81	1.0	Reference	-
Yes	32	16	173	84	0.79	0.53, 1.18	0.24
Inhalation Toxicology							
No	242	19	1048	81	1.0	Reference	-
Yes	29	17	144	83	0.87	0.57,1.33	0.52
Neurotoxicology							
No	242	19	1057	81	1.0	Reference	-
Yes	29	18	135	82	0.94	0.61, 1.43	0.23
Regulatory Policy							
No	214	18	955	82	1.0	Reference	-
Yes	57	19	237	81	0.96	0.74, 1.25	0.67
Risk Assessment							
No	143	19	616	81	1.0	Reference	-
Yes	128	18	576	82	0.96	0.74, 1.25	0.75

Abbreviations: CI, Confidence Interval; Gov't Reg. Agency, government regulatory agency; Envron, environmental; Devel, developmental

Table 4.21: Univariate analysis of political, social, and economic variables comparing respondents who completed the questionnaire (answered Q43) to respondents who dropped out in Sections 3, 4, or 5

Variable	Dropped		Completed		Odds Ratio	95% CI
	No.	%	No.	%		
Political						
Conservative	26	14	163	86	1.0	Reference
Middle of the Road	93	16	502	84	0.86	0.54, 1.37
Liberal	115	21	439	79	0.61	0.38, 0.97
Choose no Response	35	30	80	70	0.37	0.21, 0.65
Social						
Conservative	24	14	149	86	1.0	Reference
Middle of the Road	95	17	452	83	0.76	0.47, 1.24
Liberal	114	18	512	82	0.72	0.45, 1.16
Choose no Response	34	33	69	67	0.33	0.18, 0.59
Economic						
Conservative	50	14	305	86	1.0	Reference
Middle of the Road	135	19	585	81	0.71	0.50, 1.01
Liberal	50	18	228	82	0.75	0.48, 1.47
Choose no Response	32	33	64	67	0.33	0.19, 0.55

4.5.2 SOT Demographic Comparison

External validity is achieved in part by in assessing whether respondents' characteristics reflect the characteristics of the society membership as a whole. The Society of Toxicology provided general demographic information on its membership that was used to compare to those who responded to the survey. The bar graphs in Figures 4.6, 4.7, and 4.8 indicate the SOT study respondents closely match the society membership.

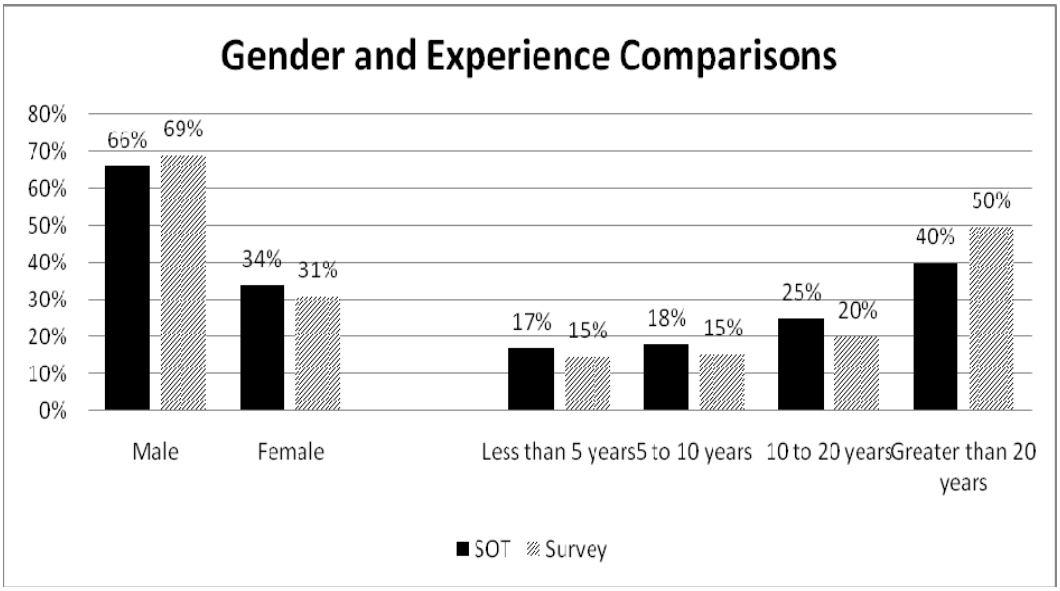

Figure 4.6: Bar chart showing gender and years of experience similarities between the SOT membership and SOT study respondents

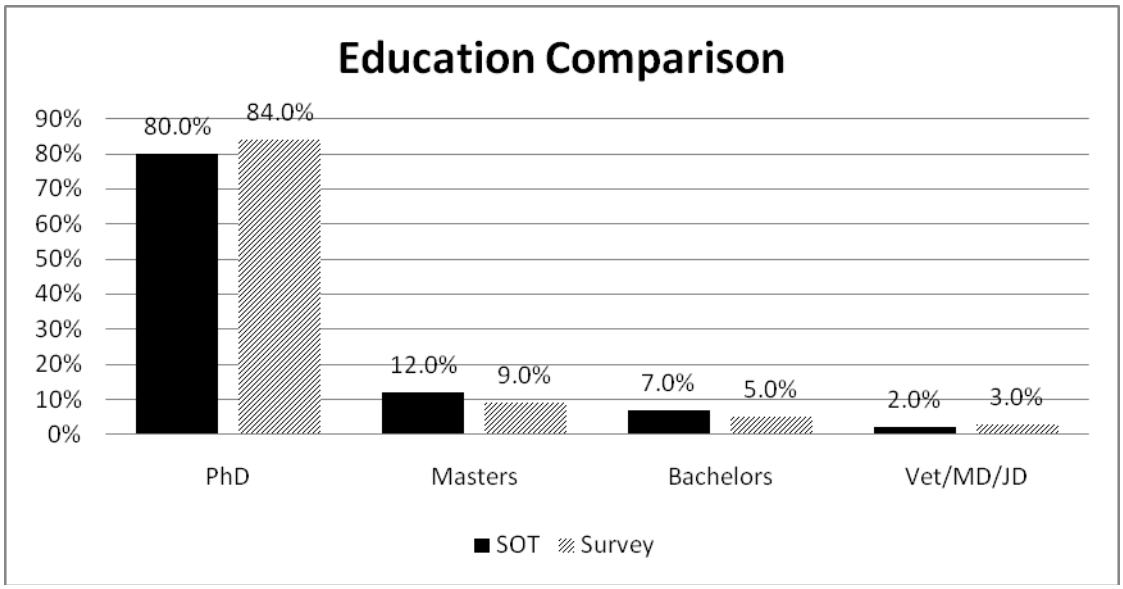

Figure 4.7: Bar chart showing educational similarities between the SOT membership and SOT study respondents

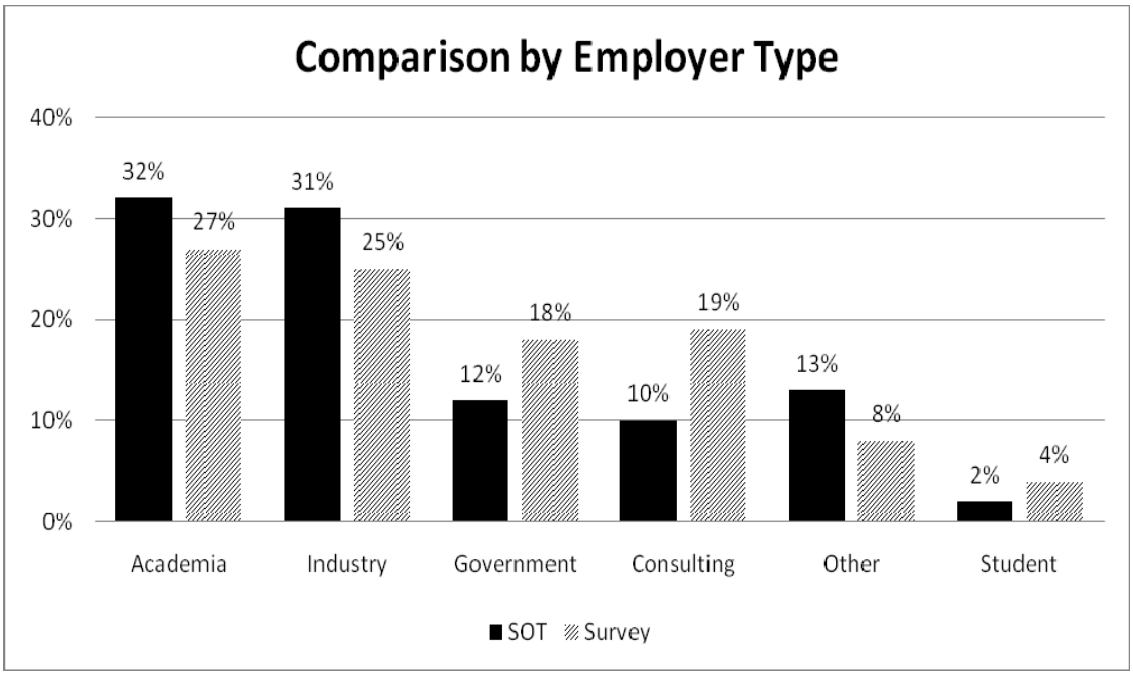

Figure 4.8: Bar chart showing employment similarities between SOT membership and SOT study respondents

4.5.3 Comparisons with Survey Information from a Similar Study of SOT

Less than three months after the Hormesis Knowledge and Opinions survey was administered to the Society of Toxicology membership, George Mason University in conjunction with the Society of Toxicology administered a census survey to those who were listed as full members of SOT to ascertain their opinions about specific chemical risks. The researchers distributed an online questionnaire toall 3,562 full members of the SOT. The survey was open from January 27 through March 2, 2009. They had a return rate of 32%. Over 200 people dropped the survey after completing the demographic

section for an adjusted response rate of 26%. Their overall findings were based on responses of the 937 who continued after the demographic section. The George Mason researchers kindly provided their demographic data to this investigator for comparison. Unlike the George Mason survey, the Hormesis survey was distributed to all SOT members, including students. In order to make similar comparisons, the student members and members with < 5 years of experience (representing associate members) were dropped from the hormesis survey. Overall the two surveys are remarkably similar on most criteria as shown in Figures 4.9, 4.10, 4.11. Comparisons for gender, age and regional demographics are virtually identical (Figures 4.9, 4.10). The areas of employment do not match exactly but are similar. The lack of an exact match may be because the hormesis survey respondent was able to check all the employment types and specialties that applied, whereas the George Mason/SOT survey respondents were restricted to selecting one category that best described the respondent.

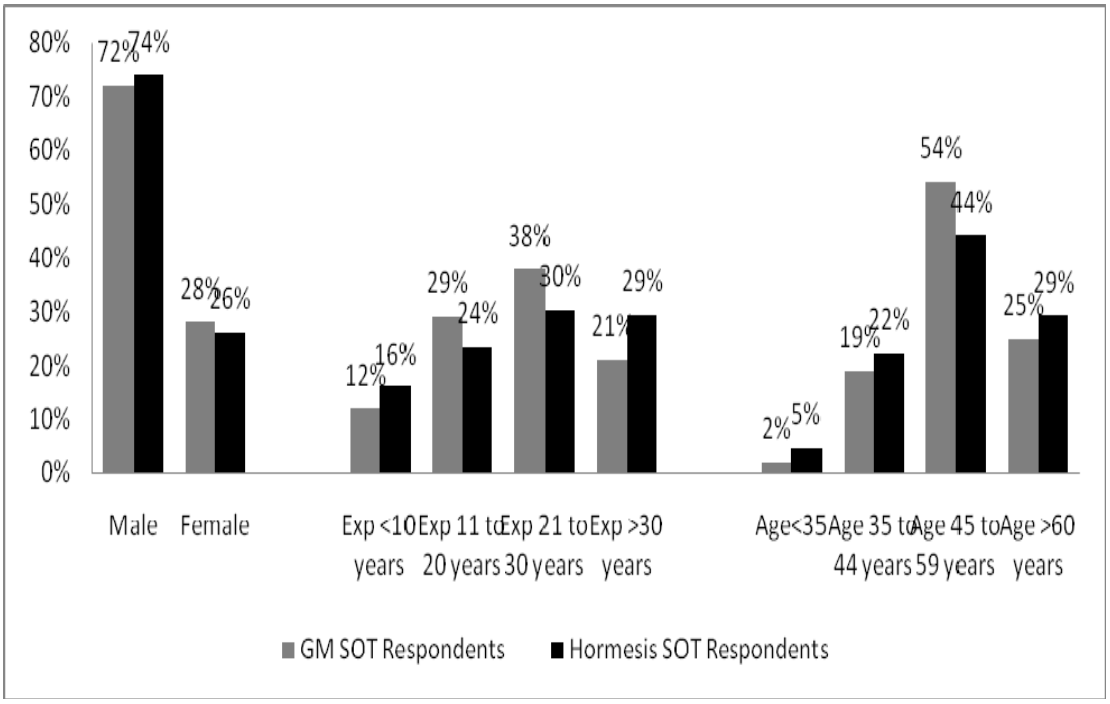

Figure 4.9: Comparison of the George Mason survey demographic data with the Hormesis Survey demographics

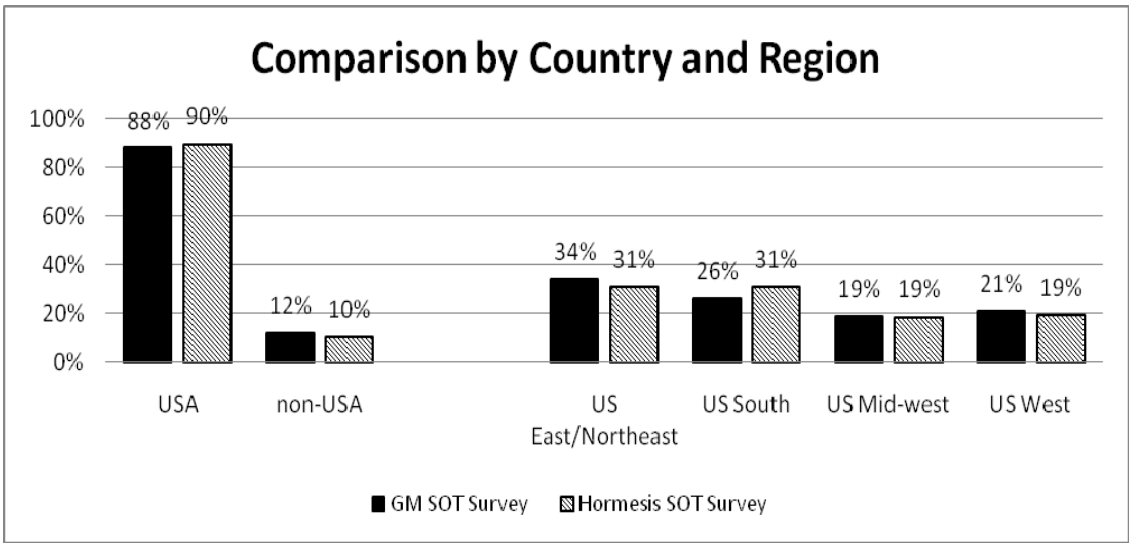

Figure 4.10 Comparison of the George Mason survey regional representation with the Hormesis Survey respondents

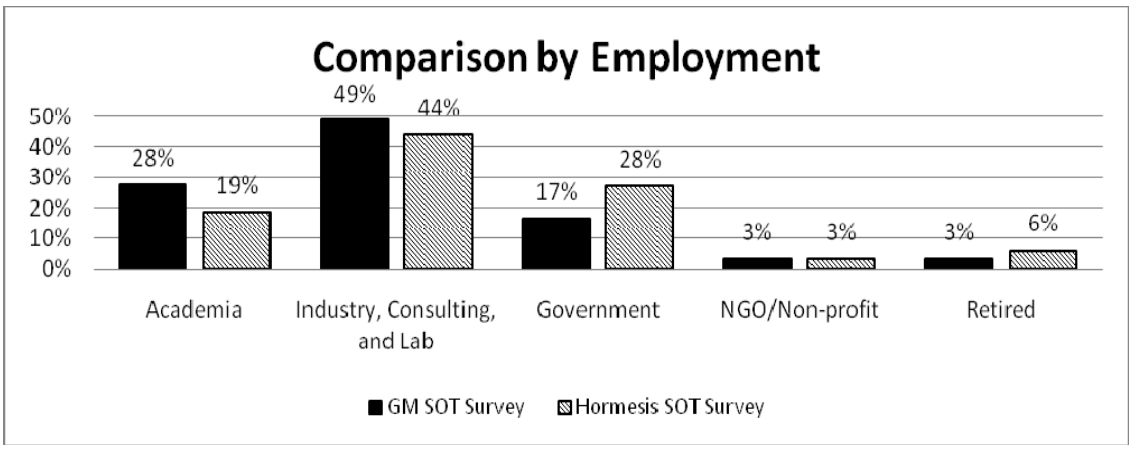

Figure 4.11: Comparison of the George Mason survey employment areas with the Hormesis Survey respondents

4.5.4 Evaluation of Responses

The research committee suggested coding comments to Questions 36, 45 and 46 as to whether they were negative, neutral, or positive toward hormesis in an effort to indirectly evaluate response bias. The results are summarized in Figure 4.12. For the purposes of this study, if comments were overwhelmingly positive or negative, over 20% in either direction, it was concluded response bias could be present. If however, the overwhelming majority of comments, 80%, were neutral then it was concluded response bias may be low. For question 36 only 7% of responses were coded as negative. This is a significant result because this question, above all others was predicted to elicit a negative response. A discussion of some of the more interesting responses is included in Chapter 5. Question 45 was a request for comments about content that may have been missed, 81% of comments were coded neutral, 11% were negative, and 8% were positive. Eleven of the 38 negative comments indicated the respondent thought the survey was biased to favor hormesis. Question 46 was a request for information about what could

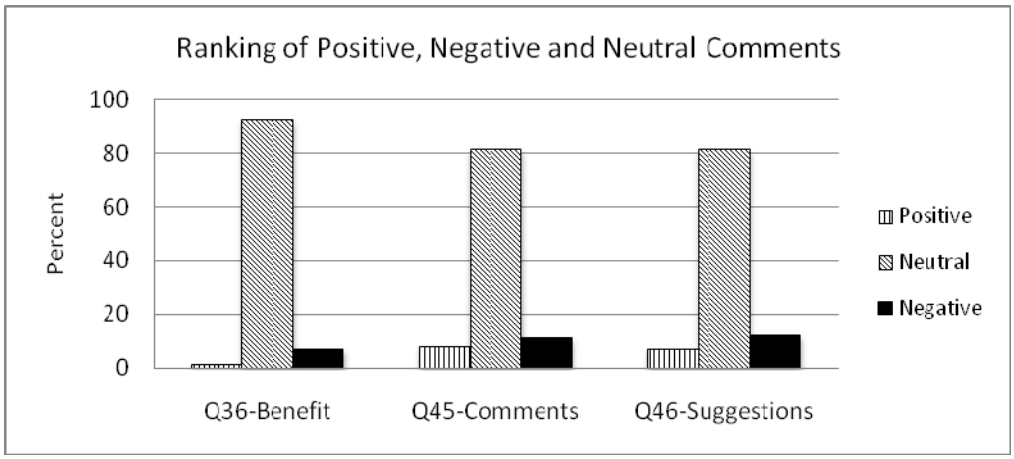

Figure 4.12: Positive, neutral and negative comments of questions 36, 45 and 46 indicating that most comments were neutral, meaning they were informative rather than critical

have been done to make the survey better. 81% were coded neutral, 12% were negative, and 7% were positive. Nine of the 39 negative comments indicated the respondent thought the survey was biased toward hormesis. For both questions 45 and 46, approximately 10% of the neutral comments were suggestions to use Likert-type rating scale rather than the dichotomous scale employed in the survey.

CHAPTER 5

DISCUSSION

5.1 Introduction

The goals of this first-ever survey of the acceptance and understanding of the hormesis dose-response concept among toxicologists and risk assessors were to ascertain attitudes on hormesis and other dose-response models; and to identify how the level of acceptance or rejection of hormesis is related to knowledge of or experience with hormesis, predisposing values, or demographic characteristics. This chapter begins with a discussion of the major findings related to the research goals, followed by a discussion of study limitations.

5.2 Major Findings

A primary rationale for this study was to determine whether toxicologists and risk assessors believe that hormesis commonly occurs across biological systems, endpoints, and chemical classes as has been reported in reviews of the literature (Anderson, 2005; Calabrese and Baldwin 2001a,d; Calabrese and Blain, 2005; Cook and Calabrese, 2006 a); or whether the survey respondents believe that hormesis dose-response is a rare event (Mushak, 2007; Thayer et al., 2005). Contrary to expectation, 50% of the respondents indicated they believe sufficient data presently exist to support the view that hormesis occurs across a wide range of species and endpoints. The fact that half of the respondents accept the broad generalizability of hormesis is notable because, aside from the published literature, hormesis is ignored or rejected outright by regulatory agencies (USEAP, 2004). The survey further indicates that most respondents have not taken

advantage of the few training opportunities available for hormesis; 90% of respondents indicated they never attended a hormesis workshop and 93% indicated they had never attended a conference on hormesis. Furthermore, 75% had never received any classroom instruction on the topic.

The finding is even more striking when one considers not just small number of respondents attending learning opportunities, but also the relative lack until recently of published studies reporting a hormesis dose-response. It is possible that the proliferation of recent publications may have had an impact on respondent opinions on the generalizability of hormesis. A search of the Web of Science ® database shows that citations of the keywords hormesis or hormetic occurred at approximately 15 per year throughout the decade of the 1980's, then in the 1990's the citation rate slowly increased, ending the decade with a total of 200 citations for the year 1999. Citations increased rapidly in the current decade and finally doubled from 1,100 citations in 2006 to over 2,200 in 2008.

Interestingly, characteristics of the respondents such as: years of experience, the society of membership, level of education, place of residence, most types of employment (excluding government and pharmaceutical companies), and political, economic or social views did not have a direct influence on their opinion on the broad generalizability of hormesis.

One of the largest influences on willingness to take hormesis into consideration as a valid biological model of dose-response was experience with hormesis based on actual research. Seventy-nine percent of subjects who reported observing the hormesis dose-response commonly in their studies agreed with the statement that hormesis is broadly

generalizable across multiple species and biological endpoints. Indeed, commonly or occasionally observing hormesis in one's own research had a profoundly positive impact on respondent's opinions on all of the policy questions.

Only two groups of respondents were found to be statistically significantly less supportive of the statement that hormesis occurs widely across species and endpoints: women (43% agreed) and those employed by the pharmaceutical industry (37% agreed). The variables were tested for correlation and were found to be independent and not correlated with any other variable, including social and political leanings. The open-ended comments made by women (n=42) indicated they did not reject the concept of hormesis per se, but thought sufficient data do not exist to support broad generalizability at this time.

The finding that only 37% of those employed by pharmaceutical companies agreed that hormesis occurred across the broad biological spectrum was unexpected. Indeed, prior to the study, it was hypothesized that this group would be much more likely to subscribe to the view that hormesis is common across multiple species and endpoints. This *a priori* assumption was made because much of the dose-response data in the published literature are derived from studies of pharmaceutical agents (Calabrese and Blain, 2005). Additionally, two issues of the journal *Critical Reviews in Toxicology* (McClellan, 2001, 2008) dedicated to hormesis present the results of a large number of pharmaceutical research studies demonstrating the hormesis dose-response. Because the finding was unexpected the comments were evaluated. Among the open-ended comments of those who disagreed (n=18), most stated that although hormesis is frequently detected in pharmaceutical research, the studies are not sufficient to support

the view that hormesis occurs in all species and biological responses across multiple agents and stressors.

Ironically, strong support for including an evaluation of public health benefit was shown by those employed by the pharmaceutical industry (60%). This high level of support is an interesting juxtaposition to the group's seeming rejection of the statement that hormesis is broadly generalizable. However, this may be explained when one considers the objective of drug discovery is to evaluate multiple doses in a more or less linear fashion of promising formulations in order to identify the beneficial zone for therapeutic impact, while at the same time establishing drug safety by identifying adverse reactions, which are typically dose-related. Simply put, drug discovery is to promote successful treatment while minimizing harm. The fact that benefit or harm may occur at low doses is clearly important to this group.

Despite the fact that EPA (2004) has explicitly excluded from risk assessment the analysis of public health benefit associated with low-dose exposure, 59% of respondents indicated that the potential for hormesis benefit should be included in a risk assessment. These findings suggest that toxicologists and risk assessors are willing to consider biological realities rather than conventional mathematic models such as the linear or threshold.

Support for including an analysis of benefit was found across most of the surveyed population. The only group that strongly disagreed (68%) with evaluating potential for public health benefit was EPA employees. This suggests that EPA policy may have biased their views, or that the institutional structure in place has reduced the range of acceptable thought within the agency.

Strong desire on the part of a majority of respondents (59%) to modify risk assessment in order to evaluate potential benefits at low doses may indicate that respondents would welcome the opportunity to analyze multiple dose response curves instead of forcing the data to fit default models that may or may not represent the biological reality. Groups strongly supportive of the ability to consider benefit (60% or greater agree) were academics, those employed by industry, members of the Society for Risk Analysis, political and social conservatives and moderates , environmental and toxicological consultants, pharmacologists and regulatory policy specialists.

The only group other than government regulatory agencies, specifically EPA, in disagreement with changing risk assessment procedures to examine potential public health benefit from hormesis was the group identifying with a specialty of neurotoxicology. 47% of respondents in this group agreed with modifying risk assessment to identify benefits. This finding appears to be unusual given the general finding that the hormesis dose-response not only dominates the field of neuroscience research but is the basis for many therapeutic agents for neurodegenerative diseases. Many of the therapeutic agents for these diseases rely on a beneficial low-dose stimulatory response (Diamond, 2008; Kastin and Pan, 2008; Mattson, 2008). An explanation may be found in the fact that neuroscience studies rarely report findings as hormesis; instead the researchers rely on a variety of dose-response descriptions including U-shaped, bell curve, biphasic, bitonic, and others (Calabrese, 2008). Researchers could simply be unaware of the concept of hormesis as it relates to their study results. Alternatively, respondents may be employing a cautious self-revisionist epistemic approach to hormesis as suggested by some neuroscience experts (Giordano et

al., 2008). The open ended comments provided by neurotoxicologists who disagree with including an analysis of benefit in risk assessment (n= 32) indicate that the explanations proposed by both Calabrese (2008) and Giordano et al. (2008) may be true. Most indicated biological systems were too variable and therefore incorporation of benefit was not warranted, others indicated they selected to disagree because not enough data existed, while a few indicated they did not completely understand the utility of hormesis for determining benefit or harm.

In fact, the rest of the open ended comments about the concept of incorporating hormesis into risk assessment followed the tenor of responses from the neurotoxicologists. None of the comments espoused passionate or extremely negative opinions about hormesis as expected. The vast majority (93%) of those providing comments about the concept of benefit were explaining their answers and they too tended to focus on population variation, the desire for more data, or the desire to know more about hormesis before agreeing. The few negative responses focused on perceived dangers of assuming benefit and concern about the creation of an "industry loophole." However, none of the comments was passionately for or against the concept which indicates that most toxicologists and risk assessors are seeking a rational, data-driven approach to risk assessment that incorporates all available data and is sensitive to biological complexity.

The finding of support for evaluating benefit is validated by the finding that a majority of all respondents (65%) are in favor of modifying hazard assessment protocols to identify the presence of hormesis. This opinion was held across all sectors, regardless of demographic characteristic, years of experience, employment history, politic, social, or

economic views, or any other characteristic. Even those employed by government regulatory agencies and neurotoxicologists who were against applying hormesis to obtain a public health benefit were in favor of designing studies that could identify the presence of the hormesis phenomenon. In particular, neurotoxicologists are strongly (67%) in favor of modifying study designs to identify whether the hormesis dose-response is present.

Because all groups agreed (93%) on the definition of hormesis that states the dose-response exhibits biological responses at low doses that are opposite to those observed at high doses and because all groups agree hormesis could be either beneficial or harmful (71%) it is consistent that such a large majority (65%) would be supportive of modifying dose-response studies (sample size, number and timing of doses) to determine whether hormesis was present. In addition, support for modifying dose-response assessments to identify hormesis has been expressed by a variety of researchers representing diverse areas of specialty. The scientists state that research efforts should be redirected from looking only at adverse effects at high doses and adjusted to be able to identify whether adverse or beneficial biological effects are occurring at heretofore unstudied lower doses (Kastin and Pan, 2008; Stumpf, 2006; Thong and Maibach, 2007). Indeed, the support for modifying dose-response study designs suggest that respondents are interested in conducting thorough dose-response assessments capable of clearly delineating the true shape of the dose response.

The final major result is that 75% of respondents indicated current regulations should be re-evaluated if hormesis were accepted as the default model for risk assessment. Not surprisingly, subjects who were ever employed by a government

regulatory agency were somewhat less likely to agree (69%) but, 69% is still a large majority of the group. Although this was a hypothetical question, using the word "if" as a request for the respondent to speculate, a very specific conclusion can be drawn from the response: toxicologists and risk assessors appear to be willing to reexamine their research methods, and study designs, as well as the risk assessment paradigm. They may be in agreement with Giordano et al., (2008) who point out that as knowledge grows, empirical evidence must direct what is studied, how it is studied, and how the results are interpreted in the future.

Overall the survey results provide an important snap-shot of toxicologists' and risk assessors' knowledge about the science of risk assessment and hormesis, and their opinions on the policies used by regulatory agencies to interpret the science. The hormesis dose-response appears to be gaining acceptance as a legitimate biological phenomenon worthy of attention. The detailed chi-square and logistic regression analyses revealed that no single demographic or personal characteristic among the over 50 studied was routinely or dramatically associated with the respondents acceptance or rejection of hormesis as a biological concept in risk assessment. A majority of the scientists who took this survey appear to be guided by science and not predisposing beliefs.

The fact that 1,247 subjects took on average 30 minutes of their time to complete the entire 44 question technical survey and in many cases provide detailed and thoughtful comments supports the idea that interest in hormesis is growing, as is a re-examination of the underlying assumptions of risk assessment model in general. The field of risk

assessment may truly be at a point where scientists are willing and eager to explore models that reflect the true biology of dose-response.

5.3 Limitations

An opinion survey of this type is not without its limitations. High survey response rates help ensure survey results are representative of the target population. The anticipated response rate for this email-based internet survey was 25% based on the literature for email delivered surveys (Hamilton, 2003; Kaplowitz et al., 2004). The return rate, meaning those who clicked on the email invitation and opened the survey, was 23% for the Society of Toxicology (SOT), close to what was expected. However the SOT adjusted response rate after removing those who completed the demographics section and did not continue was 18% representing 1,045 individuals, lower than hoped. The Society for Risk Analysis (SRA) return and response rates were much lower at 16% and 12% respectively. This was expected because of a limitation in the sampling frame which consisted of a large fraction of risk management professionals such as aviation and infrastructure professionals who have no knowledge of chemical or radiation risks. For some survey research studies, a low response rate such as the one experienced by this study may be considered problematic and give rise for concern about non-response bias. However, for this particular survey, the concerns for non-response bias may not be warranted because those respondents were representative of the societies from which they were derived. SOT respondents were used to evaluate external validity because the SRA did not supply comparative data and because of the sampling frame issues mentioned earlier. The demographic characteristics of the SOT respondents are nearly identical to

the demographic characteristics of the society as a whole. The comparative data are considered highly reliable because they were supplied by SOT and were derived from membership applications. In addition, the characteristics and responses of the present hormesis survey respondents are nearly identical to SOT members who responded to a survey on Risk Communication administered by George Mason University researchers three months after the hormesis survey closed. The George Mason survey had an adjusted response rate of 26% (n=937 SOT full members). The respondents to the two surveys who were full members of SOT were closely matched with respect to gender, years of experience and average age. Comparisons by country and region of residence in the United States are identical. The only differences between the two surveys were in the area of employment. The hormesis survey had 9% fewer academics, but 11% more respondents employed by the government.

The internal measures also suggest bias may be low. No substantial differences exist between those who started the survey and those who finished. The only notable difference was that members of SRA dropped out of the survey at a slightly higher rate than SOT members. This may be expected due to the sampling frame issues previously described. Over twenty SRA members took the time to send an email to the link provided on the invitation, to indicate that they were not familiar with chemical risk assessment or the concept of hormesis and therefore declined to take the survey. No SOT members sent emails indicating they were not familiar with the topic.

The final limitation is one found in all surveys, the concern that respondents understand the meaning and intention of the question. A few of the open ended comments indicated that in some instances respondents did not understand what was

being asked by a particular question or meant by a specific term. However, these comments were made mostly on the definition questions, for which some of the respondents did not know whether the survey was asking for the regulatory definition or their opinion. The definition questions did not impact the analysis of overall opinion. Finally, many respondents indicated the survey would have been better if it had provided the respondent with a Likert scale instead of the dichotomous responses. Admittedly, the respondent was not informed in the Introduction or in the body of the surrey that the instrument was designed to elicit responses that were not neutral or that would require reclassification to accommodate statistical analysis.

None of these limitations are likely to adversely affect in a serious manner the conclusions of this study. It is likely that these results are in fact generalizable to the broader population of toxicologists and risk assessment professionals. The phenomenon of hormesis appears to be recognized as a biological fact that should be seriously considered when designing, conducting and interpreting future risk assessments.

CHAPTER 6

CONCLUSIONS

The goals of this study were to: 1) ascertain attitudes about hormesis and other dose-response models; 2) identify whether the level of acceptance or rejection of hormesis is based on knowledge of hormesis, existing social and political values, or demographic characteristics; 3) evaluate potential for response bias; and 4) establish research priorities for hormesis.

An examination of the study participants' answers to the survey questions indicates that a majority of toxicologists and risk assessors are knowledgeable about the hormesis dose-response and in fact accept it as a phenomenon worthy of scientific exploration and consideration. Further, respondents demonstrated through their responses a strong desire to advance the science of risk assessment by taking into consideration dose-response models and research results that more accurately reflect the complexity of various biologic systems rather than employing an *a priori* default model that results in predictable, linear, non-threshold outcomes.

Level of acceptance or rejection of hormesis among the scientists who participated in this first- ever survey on the topic of hormesis was not explained by any of the characteristics or predisposing values examined in this study, with the exception of employment in government regulatory agencies or pharmaceutical companies. It was speculated *a priori* that many non-scientific aspects of a participant's background including gender, education, work experience, membership in professional societies, socio-economic and political views, employment history, and toxicological specialty, may materially affect his/her opinion of hormesis and its utility in risk assessment.

Therefore, data were collected on over 50 variables defining the above characteristics and none was predictive of a profile of who would generally be open to either accept or reject hormesis as a dose-response phenomenon. It was found unexpectedly that only employment by a government regulatory agency was consistently predictive of a respondent being less accepting of hormesis. Prior to the survey, this researcher speculated that socio-economic and political views and gender would be consistently associated with respondent attitudes about hormesis and risk assessment. Specifically, it was thought that respondents with more liberal views and women would be less accepting of hormesis as a dose-response model for risk assessment because the concept is not entirely consistent with the now widely accepted precautionary principle, which asserts that conservative protective measures must be taken when cause-and-effect relationships have not been established, but only suggested by inconclusive studies. However, the data show that most respondents appear to be willing to follow the scientific evidence of discovery and investigation with regard to dose-response research and not be influenced by existing political or social views or belief systems.

The survey clearly showed that those ever employed by government regulatory agencies and those employed by pharmaceutical companies do not accept hormesis as a widely generalizable phenomenon or a useful dose-response model. Furthermore, respondents employed by government regulatory agencies had consistently more negative opinions toward hormesis as a dose-response model. It has been speculated that for government workers this difference may be due to bias based on agency policy or agency culture. It could also be due to self-selection by those more likely to agree with the

default dose-response model and the precautionary principle, who select for employment in the regulatory environment.

The influence of non-response bias was evaluated through several internal and external measures while keeping to the study promise of maintaining respondent anonymity. Despite the lower than hoped for response rate, but because of the relatively robust external validity measures for Society of Toxicology members, it is concluded that respondents' opinions are likely a reasonable representation of the societies of which they are members.

Certainly a better understanding of hormesis and the desire to conduct studies that elucidate the full range of biological responses will likely lead to adoption of different strategies for evaluating dose-response as it applies to risk assessment, toxicology and pharmacology. The survey results indicate that scientists are prepared to direct research away from the *a priori* default models for evaluating adverse health effects at high doses and begin to characterize and reflect the complex biological effects, both adverse and beneficial, that may occur at low-levels of exposure. If this new approach or paradigm of dose-response research takes root and grows, a follow-up survey of the present study population may be in order.

Any future survey design should separately evaluate the knowledge and science of dose-response from the regulatory approach to dose-response investigations in order to avoid conflating science with public policy, which is often not scientifically based.

In conclusion, in order to truly understand how attitudes toward dose-response evolve over time, a prospective cohort study could be initiated in cooperation with the Society of Toxicology that administers a survey instrument similar to the one used in this

study to student members of the Society with periodic follow-up to evaluate change in attitudes and opinion according to the various characteristics examined in the present investigation. Such a study would be valuable for understanding the level of acceptance of the hormesis dose-response paradigm and for documenting changes in attitudes about and the conduct of risk assessment, and what factors affect these changes in attitudes.

APPENDIX A

SOCIETY OF TOXICOLOGY DEMOGRAPHIC INFORMATION

REQUEST LETTER

Amy C. Jones
Environmental Health Sciences, Morrill I, N344
University of Massachusetts
Amherst, Massachusetts 01003

April 7, 2009

Dr. Kenneth S. Ramos
President, Society of Toxicology
1821 Michael Faraday Drive, Suite 300
Reston, Virginia 20190

Dear Dr. Ramos:

I am a Full Member of the Society of Toxicology and member of the Society's Carcinogenesis; Ethical, Legal and Social Issues; Occupational and Public Health; and Risk Assessment Specialty Sections. I am also a doctoral student at the University of Massachusetts doing work on biological responses at low dose. In particular, I am interested in the hormesis dose-response phenomenon. Last September, I surveyed Society of Toxicology and Society for Risk Analysis members about their knowledge and opinions on the hormesis dose response model. The responses to the survey comprise the basis of my PhD thesis.

The goals of the survey were to 1) ascertain respondents' attitudes about various dose response models, including hormesis; 2) determine the characteristics of people who would, if allowed by the regulatory framework, take the potential for hormesis into account when designing and/or interpreting risk assessments; and 3) identify whether the level of acceptance or rejection of hormesis is based on scientific/educational training of the subject; predisposing social and political values; or demographic characteristics.

I would like to evaluate the potential for response bias in my survey by comparing the demographic characteristics of respondents who completed the survey with the overall demographic characteristics of SOT membership. Without the overall SOT membership distribution data, it will be impossible for me to assess response bias in a valid manner; and any inference I draw on my survey's results thus would be severely limited.

SOT requests its members to voluntarily provide the following information that would be very helpful to my research:

- Gender
- Highest Degree
- Years of Experience
- Employment: Academia, Contract Research Organization, Government, Industry, Military, Not Employed, Other, Research Institute, and Student

- Areas of Interest: General Toxicology, Reproductive and Developmental, Drug Discovery, Biotechnology, Carcinogenesis, Food Safety, Biological Modeling, etc.

I am requesting the Society provide me a summary of the above referenced demographic data. I do not require personally identifiable information, just the overall frequency distribution data for each demographic category. I will then compare the distribution of the above characteristics with the characteristics of my respondents in order to assess response bias.
I thank you in advance for your kind attention to this request.

If you would like to speak to me directly, please do not hesitate to call me at 301-758-0547. My email address is amyn@schoolph.umass.edu.

Sincerely,

Amy Jones

APPENDIX B

SURVEY E-MAIL INVITATION

Dear Colleague,

I am a graduate student at the University of Massachusetts at Amherst, completing a Ph.D. thesis on the hormesis dose-response. I invite you to participate in my research by completing this survey to assess knowledge and opinions about dose response in general, and hormesis in particular.

This survey is completely anonymous. Your responses will not be identified with you personally. Responses will be assessed in aggregate only.

The link to the survey is:
http://www.surveymonkey.com/s.aspx?sm=n8uQQTBqX2wZ_2fweuyMfGAw_3d_3d

The Institutional Review Board (IRB) at the University of Massachusetts Amherst has approved this study. If you have concerns about this study you may contact me directly by email at amyn@schoolph.umass.edu or by phone at 301-758-0547. Alternatively, you may contact the University's Human Research Protection Office via email at humansubjects@ora.umass.edu or by phone at 413-545-3428.

Final Survey results will be posted on the UMASS Environmental Health Sciences website at the completion of the study.

You may withdraw from the survey at any time and may choose not to answer all questions.

I appreciate your taking the time to complete this survey.

Sincerely,
Amy C. Jones

APPENDIX C

DOCUMENTATION OF SURVEY INSTRUMENT FINAL TEXT

No.	Question	Purpose
	Section 2	**The purpose of this section is to obtain information on age, sex, level of education, employment history, and/or geographical region**
1	If you have taken this survey previously, please skip to the end.	Potential respondents could have reveived more than one link depending on society membership.
2	Residence	Obtain important demographic information
3	Age	Obtain important demographic information
4	Sex	Obtain important demographic information
5	Degrees	Obtain important demographic information
6	Employers	Obtain important demographic information
7	Specialties	Obtain important demographic information
8	Yrs Exp	Obtain important demographic information
9	Memberships	Obtain important demographic information
10	Info Sources	Obtain important demographic information
11	Social	Obtain important demographic information
12	Economic	Obtain important demographic information
13	Political	Obtain important demographic information
	Section 3	**The purpose of this section is to assess your general knowledge about dose-response assessment and various dose response models.**
14	Dose-response assessment is a necessary foundation for understanding risk assessment.	Dose-response is the foundation for toxicology. Do the respondents think is is also the foundation for risk assessment?
15	Regulatory upper-bound characterizations used in cancer risk assessments provide accurate estimates of the probability of developing cancer at low doses.	Risk assessments performed pursuant to certain regulatory frameworks require specific models to be applied to the data. Do the respondents agree with an example of a default model?
16	Exposure to a genotoxic carcinogen, no matter how small, theoretically results in an increased cancer risk.	Regulatory framework question. Do the respondents agree with the current regulatory framework for assessing genotoxic compounds?

APPENDIX C (CONTINUED)

17	Exposure to non-genotoxic carcinogen, no matter how small, theoretically results in an increased cancer risk.	Regulatory framework question. Do the respondents agree with the current regulatory framework for assessing non-genotoxic compounds?
18	Exposure to ionizing radiation (e.g. X-Rays), no matter how small, theoretically results in increased cancer risk.	Regulatory framework question. Do the respondents agree with the current regulatory framework for assessing ionizing radiation?
19	The linear model employed in cancer risk assessment overstates risk in the low dose zone.	Regulatory framework question. How do the respondents interpret output from the LNT model?
20	The threshold dose-response assumes no treatment related responses occur below the estimated threshold.	Knowledge question. Do respondents agree to the text book definition of a threshold dose-response?
21	The linear non-threshold (LNT) dose-response assumes a biological response is directly proportional to dose in the low dose zone.	Knowledge question. Do respondents agree to the textbook definition of linear non-threshold (LNT) dose-response.
22	The hormesis dose-response exhibits biological responses at low doses that are opposite to those observed at higher doses, leading to either a J-shaped or inverted U shaped dose-response curve.	Knowledge question. Do the respondents agree to the definition of the hormesis dose-response commonly published in the literature?
23	For effects other than carcinogenisis, most toxicants act in a manner consistent with the following model:	Regulatory framework question. Which of the two regulatory dose-response models plus hormesis do the respondents prefer for evaluating most toxicants?
24	Carcinogens typically act via the following dose-response model:	Regulatory framework question. Which of the two regulatory dose-response models plus hormesis do the respondents prefer for evaluating most toxicants?
25	Have you ever conducted experimental research in dose-response?	How many people who answered the survey have actually conducted dose response research?
26	In my research…	Of the people who evaluate dose-response studies, how many have observed the various dose-responses listed?

APPENDIX C (CONTINUED)

	Section 4	The purpose of this section is to assess your level of familiarity with hormesis.
27	Have you ever attended a seminar, workshop, or classroom presentation on the topic of hormesis?	Personal instruction and scholarly discourse on hormesis is increasingly available. How many respondents have experience with these sources of information?
28	How commonly do you think hormesis is observed in,	A research goal is to identify research gaps. This question is intended to find out how commonly respondents think hormesis occurs in various types of studies.
29	If you answered uncommon, rare, artifactual, or do not know, to the preceding question, is it because you believe one of the following?	This follow-on question asking why the respondent answered in a particular way is important. Responses to this question will help identify whether the survey has strong response bias. If high number of does not apply, response bias favorable to hormesis may be present.
30	Any reproducible biological response to a toxic chemical or radiation exposure qualifies as an "adverse effect".	A key component of the hormetic dose response is that biological effects at low doses could be either beneficial or detrimental depending on the shape of the curve and biologic endpoint. How many respondents believe all measurable effects are adverse?
31	If a study reliably shows a J-Shaped dose response curve, it implies low dose effects could be beneficial	How do respondents interpret the J-shaped hormesis dose-response?
32	Sufficient data exist to suggest hormesis occurs in a wide range of species and endpoints following low-dose exposure to a broad range of chemical agents and physical stressors.	How many respondents agree with data on the occurrence of hormesis recently published review articles by Calabrese and others?
33	If study reproducibly demonstrates the hormesis dose-response, the implication for low doses would be:	Do respondents understand the nature of the J and inverted U shaped curves?

APPENDIX C (CONTINUED)

	Section 5	**The purpose of this section is to obtain your opinion on risk assessment principles and assess how you interpret dose response models in conducting risk assessments.**
34	What is your perspective on current state of chemical regulation?	Regulatory policy question. What do respondents think of the current state of chemical regulation?
35	What is your perspective on current state of ionizing radiation regulations?	Regulatory policy question. What do respondents think of the current state of ionizing radiation regulations?
36	Risk assessment procedures should be modified to obtain potential benefits associated with hormesis.	Regulatory policy question. Would respondents be willing to modify risk assessment procedures if the hormetic dose response showed a protective response at low doses?
37	If a chemical exhibits a hormesis dose-response, the risk assessment should accommodate data.	Regulatory policy question. Would respondents be willing to follow the dose-response data instead of applying a default model prescribed in a regulatory framework?
38	If hormesis were accepted as the default model for risk assessment, current regulations should be re-evaluated.	Regulatory policy question. Would respondents be willing to change the regulatory decisions based on hormesis?
39	The phenomenon of hormesis justifies a change in hazard assess protocols (e.g. sample size, number of doses, timing of doses).	Regulatory policy question. Scholarly articles have been published noting that hormesis cannot be reliably detected using the standard high dose study design. Do respondents believe that hormesis is common enough to change the hazard identification model?
40	Acceptance of hormesis decreases the margin of safety in risk assessments.	Regulatory policy question. Do respondents belief that acceptance of hormesis would decrease the margin of safety in a risk assessment?
41	Hormetic model indicates that at low doses risk of disease is significantly reduced.	Regulatory policy question. How do the respondents interpret the J-shaped dose-response depicted in the figure provided?

APPENDIX C (CONTINUED)

42	If hormesis is present, the traditional use of safety factors not necessary.	Regulatory policy question. The regulatory framework requires uncertainty factors to be incorporated into derivation of the final "safe dose". Would adoption of hormesis change respondents attitudes toward safety factors?
43	If hormesis were accepted as the default model for risk assessment, current and past environmental risk assessment decisions should be formally re-evaluated?	Regulatory policy question. Would respondents be open to changing risk assessment decisions if the regulatory framework was changed to account for hormesis?
44	Risk assessments based on the hormesis dose-response could address chemical mixtures as effectively as linear and threshold based risk assessments.	Regulatory policy question. Chemicals mixtures are not regulated. Do respondents think risk assessments based on the hormesis dose response could be effective at assessing chemical mixtures?
	Section 6	**Thank-you, please take another few minutes to provide feedback on the survey, then press the submit button.**
45	Do you have any suggestions about content we may have missed?	Standard question for surveys.
46	What could we have done to make this survey better?	Standard question for surveys.

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