United States Environmental Protection Agency | Science Advisory Board (1400A) Washington, DC | EPA-SAB-RSAC-01-005 May 2001 www.epa.gov/sab

ARSENIC RULE BENEFITS ANALYSIS: AN SAB REVIEW

PANEL REVIEW DRAFT

AUGUST 9, 2001

A REVIEW BY THE ARSENIC RULE BENEFITS REVIEW PANEL (ARBRP) OF THE US EPA SCIENCE ADVISORY BOARD (SAB)

August __, 2001

EPA-SAB-01-___

Honorable Christine Todd Whitman
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: Arsenic Rule Benefits Analysis; A Science Advisory Board Review

Dear Governor Whitman:

On July 19 and 20, 2001 the Arsenic Rule Benefits Review Panel of the US EPA Science Advisory Board (SAB) met to review the EPA report EPA 815-R-00-026..

As part of the review process, the ARBRP responded to five charge questions:

Charge Question 1: *How should latency be addressed in the benefits estimates when existing literature does not provide specific quantitative estimates of latency periods associated with exposure to arsenic in drinking water?*

Charge Question 2: *How should health endpoints (other than bladder and lung cancer) be addressed in the analysis, when [existing] literature does not provide specific quantification, to ensure appropriate consideration by decision makers and the public?*

Charge Question 3: *Should reduction/elimination of exposure be evaluated as a separate benefits category, in addition to or in conjunction with mortality and morbidity reduction?*

Charge Question 4: *How should total benefits and costs and incremental benefits and costs be addressed in analyzing regulatory alternatives to ensure appropriate consideration by decision makers and the public?*

Charge Question 5: *How should uncertainties be addressed in the analysis to ensure appropriate consideration by decision makers and the public?*

Detailed answers to these questions are found in the body of the report. The major findings and recommendations are:

Charge Question 1

A central component in analyzing the benefits of reduced exposure to a carcinogen is to predict the annual reduction in cancer cases following reduction in exposure. If a population previously exposed to 50 ppb of arsenic in drinking water is exposed, beginning in 2006, to only 10 ppb, cancer risks in the population will eventually decline to a steady state level associated with a lifetime of exposure to 10 ppb. How fast this reduction in risk occurs depends on the *cessation lag* following reduction in exposure. In the report, we suggest ways in which the length of this lag could be estimated. When estimates of this lag are unavailable, several possible assumptions could be made, and the implications of the assumptions for the time pattern of reduction in cancer cases calculated. For example, the upper bound to benefits (which is the central case presented in the arsenic benefits analysis) is to assume that the steady state is reached immediately (i.e., that there is no cessation lag). However, other possible assumptions could be made and should be included in the primary benefits analysis.

Charge Question 2

The scientific literature on health effects due to arsenic exposure includes studies of a number of endpoints other than cancer, as well as studies of several cancer sites for which the risks/benefits have not been quantified (EPA 2000). The quality of these studies varies, as does the strength of evidence they provide. Nevertheless, this body of evidence is relevant for the determination of an MCL and needs to be addressed more fully. In some cases, the non-quantified effects can and should be quantified. Specifically, it appears to us that it should be possible to quantify mortality from ischemic heart disease, diabetes mellitus and skin cancer. Serious consideration should also be given to prostate cancer, nephritis and nephrosis, hypertension, hypertensive heart disease and non-malignant respiratory disease. The literature that would permit quantification of cases avoided for these endpoints is discussed in Section 2.2.2 of the report.

In cases where a dose-response function has not been estimated, it should be possible to describe, in tables such as those presented in Appendix 2.2 of this report, the key features of studies in the literature. Studies must first be selected according to well-defined criteria. The information that should be provided for each study (grouped by health endpoint of interest) includes:

- Nature of the study design
- How exposure was measured
- Range of exposures observed
- What type of statistical analysis was conducted and what confounding factors were controlled for in the analysis

In some cases the literature may be so extensive that a summary of results is required in the text of the report. This summary should focus on health endpoints that have meaning to humans (e.g., ischemic heart disease rather than electrocardiogram abnormalities), and should provide some discussion of the mechanism by which the toxin would be expected to

exert an effect. The summary should also indicate the level at which effects were observed in the studies reported and should comment on the likelihood of observing these effects at the levels relevant to the regulatory decision.

Charge Question 3

Regarding Charge Question 3, we believe that reductions in exposure should *not* be considered a separate category of benefits in a benefit cost analysis. The damage function approach to valuing benefits currently used by the Agency separates the measurement of the relationship between exposure and response (e.g., risk of fatal or non-fatal cancer) from the valuation of reductions in risk of death or illness. Epidemiologists estimate dose-response functions and economists measure the value people place on reductions in risk of death or illness. Reductions in exposure are already valued under the damage function approach when people value the reductions in the risk of death or illness associated with them. To add a separate value for reductions in exposure *per se* would be double counting.

To abandon the damage function approach and ask people to value reductions in exposure directly would force lay people to act as epidemiologists, and there is evidence that this would be difficult. Studies have shown that lay people do not view risk of death or illness as related to the size of the dose of a toxic substance received; however, the essence of modern risk assessment is to relate death and illness to size of dose received.

Charge Question 4

We applaud the Agency for presenting the costs and benefits associated with various possible maximum contaminant levels rather than presenting only the costs and benefits associated with a single standard that the Agency proposes to implement. We believe, however, that in the primary analysis (i.e., in the Executive Summary) benefits and costs should be broken down by system size. Because of the large economies of scale associated with drinking water treatment, benefit cost ratios are likely to vary substantially by system size, and this information should be made clear to policy makers and the public.

We also believe that benefits (and incremental benefits associated with different maximum contaminant levels) should be presented in physical as well as in monetary terms, and that the age distribution of cases avoided should be presented whenever possible.

Charge Question 5

Benefit-cost analyses of drinking water regulations are likely to entail uncertainties in the (a) measurement of exposure, (b) measurement of dose-response, (c) valuation of health outcomes and (d) measurement of costs. The sources of these uncertainties include measurement error (uncertainty about the average level of arsenic in tap water or of the amount of tap water consumed) as well as uncertainty about which model to use in describing the relationship between exposure and response at low doses. In general, there are two approaches to handling these sources of uncertainty—sensitivity analysis and Monte Carlo simulation. In a

sensitivity analysis various assumptions are made about the correct model (e.g., dose response function) or parameter (e.g., discount rate) to use in the analysis and results are presented for each set of assumptions. In a Monte Carlo analysis a distribution is assumed for a key parameter or set of parameters (e.g., the Value of a Statistical Life) and several hundred draws are made from this distribution. Benefits are calculated for each value of the parameter drawn. This yields a probability distribution of benefits, whose parameters (e.g., the 10^{th} and 90^{th} percentiles) can be reported.

We believe that, in the case of model uncertainty, it is appropriate to rely on sensitivity analysis; however, the assumptions underlying each sensitivity analysis should be clearly spelled out when presenting results. It is particularly inappropriate to present only the highest and lowest numbers associated with a set of sensitivity analyses, which may give the reader the false impression that these constitute the upper and lower bounds of a uniform distribution. For parameters for which it is possible to specify a distribution, Monte Carlo analysis is desirable. For example, in the case of the Value of a Statistical Life.)

General Comments on the Benefit-Cost Analysis for Arsenic

The document *Arsenic in Drinking Water Rule: Economic Analysis* makes a serious attempt at analyzing the benefits and costs of alternate MCLs for arsenic in drinking water. Many aspects of the analysis deserve commendation. These include calculating benefits and costs for different possible MCLs, presenting some breakdown of benefits and costs by system size, and presenting cost-effectiveness information (cost per cancer case avoided) that would enable the drinking water standard for arsenic to be compared to other public health programs.

We do, however, have certain criticisms of the computation of the benefits, the computation of the costs and with the presentation of the results, especially as they appear in the Executive Summary.

Computation of Benefits

1. In calculating cancer cases avoided, the primary (central case) analysis assumes no cessation lag between reduction in exposure to arsenic and reduction in cancer risk. This assumption yields an *upper bound* to the number of cancer cases avoided by any MCL. It should be noted that this assumption produces an upper bound to benefits. Furthermore, alternate assumptions regarding the length of the cessation lag should be included in the primary analysis and reported in the Executive Summary.

2. Estimates of cancer cases avoided should be broken down by age. The underlying dose-response function (Morales et al. 2000) predicts reductions in risk by age group; hence cancer cases avoided can be broken down by age group. It is important for policy makers and the public to know how many beneficiaries of a regulation are 7 years old and how many are 70.

3. We believe that it is possible to quantify more health endpoints than lung and bladder

cancers. Specifically, it appears to us that it should be possible to quantify mortality from ischemic heart disease, diabetes mellitus and skin cancer. Serious consideration should also be given to prostate cancer, nephritis and nephrosis, hypertension, hypertensive heart disease and non-malignant respiratory disease. This recommendation is, however, subject to approval by the NAS Arsenic Committee.

4. The benefit analysis should present detailed information on non-quantified health effects in the manner suggested in this report (see Section 2.2 and Appendix 2.2), rather than simply listing possible health effects.

5. Estimates of avoided non-fatal cancers should be computed in the same fashion as estimates of avoided fatal cancers. The length of the cessation lag should also be treated in a parallel fashion. It would be preferable to value avoided non-fatal cancers using an estimate provided by Magat et al. (1996) of the value of a non-fatal lymphoma ($3.6 million) rather than using the value of avoiding a case of chronic bronchitis ($610,000) which is currently used in the analysis.

Computation of Costs

1. When possible, costs should be computed using data for the systems affected by the proposed arsenic standard(s) rather than national cost data.

2. The costs of complying with the proposed MCLs may be overstated to the extent that (a) removal of arsenic may also remove other toxic substances; (b) possibilities for combining ground and surface water to meet the MCL have been overlooked.

3. The capital costs of drinking water treatment should be amortized using the interest rate that each water system must pay to borrow money, not at the rate of 7% (or 3%) used in the current analysis.

Presentation of Results

1. The Executive Summary should clearly state the size of the population affected by each MCL considered in the analysis, as well as the number of systems affected.

2. The Executive Summary should present benefits in physical as well as monetary terms, including the age distribution of avoided cancers (and other health endpoints, if possible).

3. The primary case analysis should include sensitivity to the length of the cessation lag and this should be reported in the Executive Summary.

4. Benefits and costs should be broken down and compared by system size.

We appreciate the opportunity to review and provide advice on this important report. The Science Advisory Board would be pleased to expand on any of the findings described in our report, and we look forward to your response.

Sincerely,

Dr. William H. Glaze, Chair
EPA Science Advisory Board

Dr. Maureen Cropper, Chair
Arsenic Rule Benefits Review Panel
EPA Science Advisory Board

NOTICE

This report has been written as part of the activities of the Science Advisory Board, a public advisory group providing extramural scientific information and advice to the Administrator and other officials of the Environmental Protection Agency. The Board is structured to provide balanced, expert assessment of scientific matters related to problems facing the Agency. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the views and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names or commercial products constitute a recommendation for use.

Distribution and Availability: This Science Advisory Board report is provided to the EPA Administrator, senior Agency management, appropriate program staff, interested members of the public, and is posted on the SAB website (www.epa.gov/sab). Information on its availability is also provided in the SAB's monthly newsletter (*Happenings at the Science Advisory Board*). Additional copies and further information are available from the SAB Staff [US EPA Science Advisory Board (1400A), 1200 Pennsylvania Avenue, NW, Washington, DC 20460-0001; 202-564-4546].

U.S. Environmental Protection Agency
Science Advisory Board
Executive Committee
Arsenic Rule Benefits Review Panel*

CHAIR

Dr. Maureen L. Cropper, Lead Economist, The World Bank, Washington, DC and Professor of Economics, University of Maryland
Member: Advisory Council on Clean Air Compliance Analysis

OTHER SAB MEMBERS

Dr. Richard Bull, Consulting Toxicologist, MoBull Consulting, Kennewick, WA
Member: Research Strategies Advisory Committee
Drinking Water Committee

Dr. W. Michael Hanemann, Professor, University of California, Berkeley, CA
Member: Environmental Economics Advisory Committee

Dr. V. Kerry Smith, University Distinguished Professor, Department of Agricultural and Resource Economics, North Carolina State University, Raleigh, NC
Member: Advisory Council on Clean Air Compliance Analysis

CONSULTANTS

Dr. A. Myrick Freeman, Professor, Department of Economics, Bowdoin College, Brunswick, ME

Dr. Dale Hattis, Research Associate Professor, Center for Technology, Environment, and Development (CENTED), Clark University, Worcester, MA

Dr. Irva Hertz-Picciotto, Professor, Department of Epidemiology, University of North Carolina, Chapel Hill, NC.

SCIENCE ADVISORY BOARD STAFF

Ms. Rhonda Fortson, Management Assistant, 1200 Pennsylvania Avenue, NW, Washington, DC, Phone: (202) 564-4563, Fax: (202) 501-0582, (fortson.rhonda@epa.gov)

Ms. Wanda Fields, Management Assistant, 1200 Pennsylvania Avenue, NW, Washington, DC, Phone: 202-564-4539, Fax: 202-501-0582, (fields.wanda@epa.gov)

Mr. Thomas Miller, Designated Federal Officer, 1200 Pennsylvania Avenue, NW, Washington, DC, Phone: 202-564-4558, Fax: 202-501-0582, (miller.tom@epa.gov)

TABLE OF CONTENTS

1. INTRODUCTION

1.1 Background

According to information provided by EPA (letter from Diane Regas, June 9, 2001), studies have linked long-term exposure to arsenic in drinking water to cancer of the bladder, lungs, skin, kidney, nasal passages, liver, and prostate. Non-cancer effects of ingesting arsenic include cardiovascular, pulmonary, immunological, neurological, and endocrine (e.g., diabetes). The current standard of 50 ppb was set by EPA in 1975, based on a Public Health Service standard originally established in 1942. A March 1999 report by the National Academy of Sciences concluded that the current standard does not achieve EPA's goal of protecting public health and should be lowered as soon as possible.

The Safe Drinking Water Act (SDWA) requires EPA to revise the existing 50 parts per billion (ppb) arsenic standard. In response to this mandate, the Agency published a standard of 10 ppb to protect consumers against the effects of long-term, chronic exposure to arsenic in drinking water on January 22, 2001. The rule is significant in that it is the second drinking water regulation for which EPA has used the discretionary authority under §1412(b)(6) of the SDWA to set the Maximum Contaminant Level (MCL) higher than the technically feasible level, which is 3 ppb for arsenic -- based on a determination that the costs would not justify the benefits at this level. The January 22, 2001 arsenic rule is based on the conclusion that a 10 ppb MCL maximizes health risk reduction at a cost justified by the benefits.

Key stakeholder concerns on the benefits component of the economic analysis include the following issues: (1) the timing of health benefits accrual (latency); (2) the use of the Value of Statistical Life as a measure of health benefits; (3) the use of alternative methodologies for benefits estimation; (4) how the Agency considered non-quantifiable benefits in its regulatory decision-making process; (5) the analysis of incremental costs and benefits; and (6) the Agency's assumption that health risk reduction benefits will begin to accrue at the same time costs begin to accrue.

The January 22, 2001 rule will apply to all 54,000 community water systems and requires compliance by 2006. A community water system is a system that serves 15 locations or 25 residents year-round, and includes most cities and towns, apartments, and mobile home parks with their own water supplies. EPA estimates that roughly five percent, or 3000, of community water systems, serving 11 million people, will have to take corrective action to lower the current levels of arsenic in their drinking water. The new standard will also apply to 20,000 "non-community" water systems that serve at least 25 of the same people more than six months of the year, such as schools, churches, nursing homes, and factories. EPA estimates that five percent, or 1,100, of these water systems, serving approximately 2 million people, will need to take measures to comply with the January 22, 2001 rule. Of all of the affected systems, 97 percent are small systems that serve fewer than 10,000 people each.

1.2 Charge to the Panel

The Science Advisory Board (SAB) was asked to conduct a review of the benefits analysis prepared by EPA in support of the arsenic drinking water standard which is contained in its regulatory support document *Arsenic in Drinking Water Rule Economic Analysis* (USEPA, 2000). The Agency asked that the Panel evaluate whether the components, methodology, criteria and estimates reflected in EPA's analysis are reasonable and appropriate in light of 1) the Science Advisory Board's (SAB) benefits transfer report (SAB, 2000, Report on EPA's White Paper, *Valuing the Benefits of Fatal Cancer Risk Reduction*), 2) *EPA Guidelines for Preparing Economic Analyses* (USEPA, 2000a), 3) relevant requirements of SDWA, 4) the *Report of the Benefits Working Group of the National Drinking Water Advisory Council* (NDWAC unpublished, October 1998), and 5) recent literature. Specifically, the Agency asked that the Panel consider the following issues:

> Charge Question 1: *How should latency be addressed in the benefits estimates when existing literature does not provide specific quantitative estimates of latency periods associated with exposure to arsenic in drinking water?*
>
> Charge Question 2: *How should health endpoints (other than bladder and lung cancer) be addressed in the analysis, when [existing] literature does not provide specific quantification, to ensure appropriate consideration by decision makers and the public?*
> Charge Question 3: *Should reduction/elimination of exposure be evaluated as a separate benefits category, in addition to or in conjunction with mortality and morbidity reduction?*
>
> Charge Question 4: *How should total benefits and costs and incremental benefits and costs be addressed in analyzing regulatory alternatives to ensure appropriate consideration by decision makers and the public?*
>
> Charge Question 5: *How should uncertainties be addressed in the analysis to ensure appropriate consideration by decision makers and the public?*

Responses to these questions, and to other issues the Committee wishes to address, are provided to the Agency below.

2. RESPONSE TO THE CHARGE QUESTIONS

2.1 The Impact of the Timing of Exposure on Avoided Cancers

Charge Question 1: How should latency be addressed in the benefits estimates when existing literature does not provide specific quantitative estimates of latency periods associated with exposure to arsenic in drinking water?

1.1.1. Introduction

A central component in analyzing the benefits of reduced exposure to a carcinogen is to predict the annual reduction in cancer cases following reduction in exposure. If a population previously exposed to 50 ppb of arsenic in drinking water is exposed, beginning in 2006, to only 10 ppb, cancer risks in the population will eventually decline to a steady state level associated with a lifetime of exposure to 10 ppb. How fast this reduction in risk occurs depends on the *cessation lag* following reduction in exposure.[1]

In order to explain what should be done when the length of this cessation lag in unknown, we must describe how the timing of the relationship between exposure and response (death due to cancer) should be treated in a benefits analysis. As in the case of arsenic, we analyze a policy that would reduce exposure from a current level of d^0 (e.g., 50 ppb) to d¢ (e.g., 10 ppb). We assume that this policy would continue into the indefinite future.

For a benefits analysis we would like to:

(A) Calculate the expected number of cancer fatalities avoided each year, as a result of the policy, beginning with the year in which the policy is enacted and continuing into the future.

If benefits are to be monetized:

(B) The expected number of cancer fatalities avoided each year should be multiplied by the value of a statistical life in that year. This will give the dollar value of benefits each year, beginning with the year in which the policy in enacted. The dollar value of benefits in each year should be discounted to the year in which the policy is enacted and summed. The present discounted value of benefits, so calculated, should be compared with the present discounted value of costs, calculated over the same period.

The timing of the relationship between exposure and cancer mortality is *implicit* in the calculations in (A). As described more fully below, if the lag between reduction in

[1] We believe that this is more appropriately termed a "cessation lag," rather than "latency." This distinction is clarified below.

exposure and reduction in risk of death is long, there will be fewer cancer fatalities avoided in years immediately following the policy than if the lag were shorter. Uncertainties in the timing of the exposure-response relationship will be reflected in uncertainties in the number of cancer fatalities reduced each year after the policy is enacted. These uncertainties should be treated as described in the answer to Charge Question 5.

2.1.2 Calculation of Reduced Cancer Fatalities Associated with Reduced Exposure to a Carcinogen

The approach taken here is to relate the age-adjusted risk of death due to cancer to history of exposure to the carcinogen. This relationship, together with information on the age distribution of the population affected by the policy, can be used to calculate the expected number of cancer fatalities avoided by the policy.

The epidemiology underlying the arsenic benefits analysis (Morales et al. 2000) assumes that the conditional probability of dying from cancer at age t, h(t) is related to cumulative exposure to a carcinogen as of age t, x_t, by a proportional hazard model:

(1) $h(t,x) = h_0(t)g(x_t)$

where $h_0(t)$ = baseline risk of dying from cancer at age t (assuming survival to age t).[2]

2.1.2.1 The Timing of the Exposure-Response Relationship

The key question is how cumulative exposure (x_t) depends on the dose of arsenic received at ages 0 through t. Let d_i = dose received at age i. A general form that this relationship could take is:[3]

(2) $x_t = f_t(d_0,d_1,...,d_t)$

The exact form of this function reflects the answers to the following four questions (Tollerud et al. 1999):

(a) How long does it take after an exposure until an increase in risk is observed?
(b) How long does the effect of an exposure last after exposure has terminated?
(c) How does the effect of exposure vary by the age at which it was received?
(d) Does the exposure act at an early or late stage in the carcinogenic process?

[2] A proportional hazard model (Pope et al. 1995) is also used to measure the association between particulate matter and all-cause mortality in *The Benefits and Costs of the Clean Air Act, 1970-1990* (USEPA 1997) and *The Benefits and Costs of the Clean Air Act, 1990-2010* (USEPA 1999). The issue of the length of the cessation lag after a reduction in exposure also arises in these studies.

[3] The function $f_t( )$ could also be conditioned on other factors such as smoking.

The relevant questions for the implementation of changes in the drinking water standard for arsenic are questions (b)-(d). In contrast, most of the epidemiologic literature addressing the issue of *latency* has focussed on question (a), which is the usual definition of latency. The committee wishes to underscore that data addressing question (a) do not necessarily provide information answering questions (b)-(d). Unfortunately, much less work has been done to evaluate questions (b)-(d) in the epidemiologic literature in general, and in the research on arsenic carcinogenicity in particular.

The NAS report *Veterans and Agent Orange: Update 1998* (Tollerud et al. 1999) addresses the second question, regarding how long effects last after cessation of exposure. With respect to arsenic in drinking water, the charge of our committee is an expansion of this question: when does the excess risk (compared to a lifetime of exposure to d′ (e.g., 10 ppb)) begin to attenuate and how long does it take until all of the excess is eliminated? Since the term latency has a traditional usage that is not the charge given to this committee, we have coined the phrase "cessation-lag" to clarify and emphasize the difference.

An important point is that the time to benefits from reducing arsenic in drinking water may **not** equal the estimated time since first exposure to an adverse effect. A good example is cigarette smoking: the latency between initiation of exposure and an increase in lung cancer risk is approximately 20 years. However, after cessation of exposure, risk for lung cancer begins to decline rather quickly. A benefits analysis of smoking cessation programs based on the observed latency would greatly underestimate the actual benefits. We return to the issue of how to estimate the length of the cessation lag below.

2.1.2.2 Calculating the Time Path of Cancer Cases Avoided

If the relationships in (1) and (2) are known, it is, in principle, a simple matter to compute the expected number of cancer fatalities avoided at age t (and, by analogy, for all other ages) in each year following the policy. In the first year of the policy it is only the most recent dose of the carcinogen (d_t for persons who are age t in the year the policy is enacted) that is affected by the policy. The expected reduction in risk of death due to cancer at age t in the first year of the policy is:

(3) $h_0(t)[g(f_t(d_0,d_1,...,d_t^0)) - g(f_t(d_0,d_1,...,d_t'))]$

where the superscripts ^{0} and $'$ refer to doses with and without the policy, respectively. In the second year of the policy, for persons of age t, both d_{t-1} and d_t are affected by the policy, and the formula in (3) would be adjusted accordingly. Eventually, a steady-state will be reached in which persons of age t face the same mortality risk from cancer as people who have been exposed to the lower level of the carcinogen (d′) throughout their lifetime.

In each year, the number of fatalities avoided by the policy among persons of age t would be the expression similar to (3) multiplied by the number of persons of age t. Similar computations would be performed for persons of all ages. In this manner, it

should be possible to compute the expected number of fatalities avoided, *by age (or age-group)*, in each year following the enactment of the policy. Because the age distribution of avoided cancer fatalities is calculated, it should be reported in a benefits analysis even if information on the age distribution of avoided fatalities is not used in valuing avoided mortality.

2.1.3 Quantifying the Relationship Between Exposure and Mortality Risk

Most epidemiologic studies ignore the time pattern of exposure in estimating the proportional hazard model in equation (1). For example, Morales et al. (2000) effectively assume that

$$(4) \qquad x_t = \sum_{i=0}^{t} d_i \ .$$

Estimating the time pattern of exposure and effect in the context of equations (1) and (2) is not trivial. In order to properly study effects of protracted exposures, detailed exposure histories for each study subject, including the dates and ages when the individual was exposed and the level of exposure at all points in time, are needed. Appropriate statistical methods have been developed for an investigation of the effect of exposure accrued as a function of time since that exposure (Thomas, 1983; Breslow and Day, 1987; Thomas, 1988). In general, the ability to investigate the issues of timing of exposure in a given data set will depend on the quality of the exposure measure, the quality of the timing of exposure information, the number of people developing the disease of interest, and variation of exposure over time within the study group. These aspects of study quality are, of course, important in evaluating any epidemiologic investigation. But there are special problems that arise in the evaluation of time-related factors (Enterline and Henderson, 1973; Peto, 1985; Thomas, 1987).

Appendix 2.1 to this report further discusses possible methods for estimating the time pattern of exposure and response. If, however, such estimation is impossible (as the charge question assumes), what can be done?

One extreme assumption that would yield an *upper bound* to the benefits of the program is to assume that the program immediately attains the steady-state result, i.e., that the reduction in the age-t mortality rate is given by:

$$(5) \qquad h_0(t)[g(f_t(d_0^{\,0},d_1^{\,0},...,d_t^{\,0})) - g(f_t(d_0',d_1',...,d_t'))].$$

This assumption is implicit the Agency's primary analysis.

In the absence of data that would make it possible to estimate the cessation lag and account for it as described above, it would still be desirable to examine the influence of this lag by performing sensitivity analyses similar to those carried out for the PM - mortality relationship in the Agency's analysis of *The Benefits and Costs of the Clean*

Air Act: 1990-2010 (USEPA 1999). The Agency assumed alternative time patterns for the reduction in mortality risk following the reduction in PM concentrations, for example, assuming an equal percentage reduction in risk each year for a 15 year period, and then calculated the present value of the stream of deaths avoided. We recommend that similar sensitivity analyses be conducted here.

2.2. Characterization of Non-Quantified Health Endpoints

> **Charge Question 2**: *How should **health endpoints (other than bladder and lung cancer)** be addressed in the analysis, when [existing] literature does not provide specific quantification, to ensure appropriate consideration by decision makers and the public?*

2.2.1 Overview

The scientific literature on health effects due to arsenic exposure includes studies of a number of endpoints other than cancer, as well as studies of several cancer sites for which the risks/benefits have not been quantified (USEPA 2000). The quality of these studies varies, as does the strength of evidence they provide. Nevertheless, this body of evidence is relevant for the determination of an MCL and needs to be addressed more fully. In some cases, the non-quantified effects can and should be quantified. In other words, the lack of quantification by EPA, to date, of these effects should not be construed to mean that they are not quantifiable.

Of the 49 non-quantified non-carcinogenic health effects listed in the Benefits Analysis (USEPA 2000), some would not be relevant at low exposure levels, e.g., at or below the current standard. These would include gangrene in adults or children, hepatic enlargement, Raynaud's syndrome and others. The main categories for which there may be concern at lower exposure levels are: several cardiovascular and cerebrovascular diseases, endocrine effects (diabetes mellitus), reproductive health outcomes, and non-malignant respiratory diseases. Some data have emerged for neurologic or neurodevelopmental outcomes, but this evidence is currently somewhat sparse.

Studies addressing the major categories of concern at lower exposure levels are listed in the tables in Appendix 2.2 (which are not comprehensive, but rather, representative). These studies demonstrate a broad array of related endpoints and indicate the range and weight of evidence, qualitatively, as well as the consistency with which these effects are related to arsenic exposure. Such consistency, particularly when at least some of the studies are of high quality and have adjusted for individual-level confounders, strengthens the evidence for causality.

Given (a) the consistency of results, including supportive *in vivo* animal experiments; (b) epidemiologic studies with individual level data on exposure, outcomes, and confounders; and (c) evidence suggesting plausibility of effects at low exposures: the Panel finds that for several of these health endpoints, the benefits can and should be quantified. These include, at a minimum, mortality from ischemic heart disease, diabetes

mellitus, and skin cancer. Serious consideration should also be given to prostate cancer, nephritis and nephrosis, hypertension, hypertensive heart disease, and non-malignant respiratory disease. The discussion below briefly assesses the broad groupings of outcomes, highlighting those for which quantification appears to be eminently feasible.[4] We also discuss in Appendix 2.2 a "public health based" approach that suggests potential order-of-magnitude effects for deaths due to other cancers and to cardiovascular disease.

The type of information that should be provided in a benefit-cost analysis about endpoints that have not been quantified is listed in the tables in Appendix 2.2. For each health endpoint (e.g., cardiovascular morbidity), studies that pass certain scientific criteria should be listed.[5] The information that should be provided for each study includes:

- Nature of the study design
- How exposure was measured
- Range of exposures observed
- What type of statistical analysis was conducted and what confounding factors were controlled for in the analysis
- Measure of association (e.g., odds ratio) and level of statistical significance of the association

In some cases the literature may be so extensive that a summary of results is required in the text of the report. This summary should focus on health endpoints that have meaning to humans (e.g., ischemic heart disease rather than electrocardiogram abnormalities), and should provide some discussion of the mechanism by which the toxin would be expected to exert an effect. The summary should also indicate the level at which effects were observed in the studies reported and should comment on the likelihood of observing these effects at the levels relevant to the regulatory decision.

2.2.2 Quantifiability of Particular Health Endpoints

2.2.2.1. Cardiovascular disease endpoints (see tables I, II, and III in Appendix 2.2).

Both human and animal studies provide evidence that arsenic affects the

[4] Notably, these outcomes are not all independent. For instance, arsenic is associated with increased prevalence of hypertension, and with increased incidence of ischemic heart disease. Within the studies assessing the latter, hypertension was a strong risk factor. Thus, hypertension may be one step along one or more pathways by which arsenic increases risk for ischemic heart disease. Nonetheless, hypertension can itself be a cause of death, though this occurs much more rarely than death due to ischemic heart disease.

[5] For an example of such criteria see Table 5-2 in *The Benefits and Costs of the Clean Air Act, 1990-2010* (USEPA 1999) which lists the criteria used to select studies that examine the health effects of the criteria air pollutants.

cardiovascular system, possibly via several mechanisms. The human studies have included both occupational cohorts for which exposure is primarily by inhalation, and communities for which exposure is primarily via drinking water. Both morbidity (Lagerkvist et al.1986, Chen et al.1988, Chen et al.1995, Tseng et al.1996, Chiou et al.1997, Rahman et al.1999, Hsueh et al.1998, Tsai et al.1999), and mortality (Axelson et al.1978, Wu et al.1989, Engel et al.1994, Chen et al.1996, Tsai et al.1999, Lewis et al.1999, Hertz-Picciotto et al.2000) have been addressed in these investigations. Several tables in Appendix 2.2 illustrate the range of types of studies and exposure levels at which these effects have been observed.

The Taiwanese study by Chen et al., 1996 on mortality from ischemic heart disease is particularly interesting, in that a wide range of individual-level confounding factors were adjusted in the analysis, including age, sex, smoking, body mass index, serum cholesterol level, serum triglyceride level, blackfoot disease, hypertension and diabetes. Their adjustment for the latter two chronic diseases that may themselves contribute to ischemic heart disease risk could have attenuated the effects, although the relative risks are reduced only modestly by the inclusion of the confounders other than blackfoot disease. Nevertheless, there is a strong dose-response relationship, rising from 2-fold to 5-fold increased risks according to the cumulative exposure level.

Another study from Taiwan, by Tsai et al. (1999), relied on vital statistics, and hence did not collect the individual-level confounding data included by Chen and colleagues. However, these authors present analyses for a broader list of causes of mortality, including diabetes, hypertension, pulmonary heart disease, cerebrovascular disease, liver cirrhosis, and a host of other non-cancer and cancer endpoints. The findings on lung and bladder cancer confirm those of numerous other investigators; results for ischemic heart disease are similarly consistent with those of Chen et al.(1996) and others. Additionally, the study presents information on some health outcomes some outcomes not previously observed in arsenic-exposed populations.

Whereas most of the studies on cardiovascular endpoints have been conducted in communities with long and heavy exposures, a few were conducted in a population with more relevant levels. For instance, Lewis et al.(1999) examined records from the Mormon Church from towns in Utah with concentrations in drinking water of 18-164 ppb. These authors found mortality due to hypertensive heart disease to be elevated in both males and females. Although individual-level confounder data were not available, the church's prohibitions on consumption of alcohol and caffeine would tend to minimize this problem; the extremely low rates of respiratory cancer and non-malignant respiratory disease attest to the low level of smoking in this population, which may also explain the low incidence of ischemic heart disease. In another study relevant for low level exposures, Gomez-Caminero (2001) examined several biomarkers of subclinical cardiovascular damage comparing a population exposed at 45 *:* g/L in drinking water to one with negligible exposures (<2 *:* g/L). Among pregnant women residing in the exposed community, the levels of von Willebrand factor were significantly reduced as compared with those in unexposed pregnant women. The important point is that these data suggest damage to the endothelium of the arterial walls at levels just under the

current standard of 50 *:* g/L. The vascular endothelium serves as a barrier between blood plasma and the arterial smooth muscle and regulates the flow of lipoproteins between these compartments. Arsenic may damage the endothelium directly or restrict its repair or regenerative capacity, by inhibiting endothelial cell hyperplasia. Reduced von Willebrand factor could play a role in this process.

It is also notable that, in the past, clinical cardiovascular effects normally only seen in adults were observed in children at very high exposure levels. The possibility that subclinical damage to the cardiovascular system occurs in early life, setting the stage for severe and potentially fatal events at older ages, should be considered.

The Panel concludes that cardiovascular effects of arsenic are plausible at current levels in drinking water. Despite uncertainty in the shape of the dose-response curve, a benchmark dose approach would be a reasonable method for estimating benefits from reduction of the MCL. To place the epidemiologic findings with regard to ischemic heart disease in context, over 500,000 deaths occurred in the U.S. in 1999 due to this cause, or 22% of all deaths. Undoubtedly the overwhelming majority of these are not due to arsenic. However, the same can be said for lung and bladder cancer in the general population. Given the large background incidence of ischemic heart disease, the committee believes these effects/benefits should be quantified. A similar argument would apply to the morbidity and mortality from hypertension.

Peripheral vascular disease is a well-established effect of high exposures to arsenic, to the extent that the presence of one severe form of this condition, blackfoot disease, has been used as an indicator of exposure. There is probably little direct relevance of the extreme manifestations of this condition for lower exposures. The likelihood of less severe conditions at low exposures is uncertain.

2.2.2.2 Diseases of the Endocrine System (see table IV, Appendix 2.2).

Most of the epidemiologic literature demonstrating increased risk of diabetes in association with arsenic exposure has been published in the last five years (Tsai et al.1999, Lai et al.1994, Tseng et al.2000, Rahman et al.1996). Studies include occupational and drinking water sources for exposure, and both mortality and morbidity studies have found significant excesses. Generally speaking, because diabetes is not a common cause-of-death, mortality studies would be expected to observe only the tip of the iceberg in terms of increased incidence. However, even when not fatal, diabetes engenders large medical costs and has a serious, lifelong impact on the quality of life.

Besides clinical disease, glucosuria and elevated glycosylated hemoglobin have both been found in association with arsenic exposure (Jensen and Hansen, 1998, Rahman et al.1999, Gomez-Caminero 2001). These are biologically significant markers of impaired glucose metabolism. Glycosylated hemoglobin represents an indicator of long-term glycemic control. The Chilean population examined by Gomez-Caminero (2001), for which exposures were ~45 : g/L, was found to have significantly elevated glycosylated hemoglobin, both when this biomarker was treated as a continuous measure

(% of hemoglobin glycosylated), and when it was dichotomized (>6.5% vs. ≤6.5%). Since these women were pregnant, the age range was fairly young and therefore the majority were born after levels were reduced to about 110 ∶g/L, which occurred around 1970 (Hopenhayn-Rich et al., 2000). As the risk of diabetes increases with age, the findings may indicate that the effects of arsenic on glycemic status could begin early, laying the basis for clinical disease that manifests primarily beyond the reproductive years (i.e., Type II diabetes).

Evidence for the diabetogenicity of arsenic is mounting, plausible mechanisms have been shown, subclinical markers of altered glycemic control have been observed, and there appears to be relevance at low exposures. Diabetes was directly responsible for 68,000 deaths in the U.S. in 1999, representing 2.9% of deaths, more than five times as many as occurred due to bladder cancer. Quantification of the benefits of reducing the arsenic MCL in terms of diabetes mortality, as well as the multidimensional costs associated with chronic illness, is appropriate. Any effect that arsenic has in increasing the incidence or advancing the onset of Type II diabetes will contribute to the risks of many other diseases associated with arsenic exposure (e.g. hypertension, cardiovascular disease, liver cancer, peripheral vascular disease).

2.2.2.3 Other cancer sites (see table V, Appendix 2.2).

Increased risks for kidney, liver, skin, bone, prostate, laryngeal, nasal and other sites are observed to occur in arsenic-exposed populations (Lewis et al.1999, Smith et al.1992, Tsai et al.1999). A comprehensive accounting of benefits from the reduction in the arsenic MCL should quantitate at least the strongest of these effects, accounting for uncertainty. Recent studies on the mechanisms for arsenic carcinogenicity do not suggest that lung and bladder would be the only sites affected. An excess of prostate cancer was associated with cumulative arsenic exposures above 1 ppm year in Utah.

2.2.2.4 Non-malignant respiratory diseases (see table VI, Appendix 2.2).

The increased incidence of bronchitis, emphysema, respiratory symptoms, and chronic airway obstruction are surprising for exposures that do not occur via inhalation. At high exposures, strong dose-response relationships were found for respiratory symptoms (Mazumder et al.2000). Plausibility for these effects at low exposures is uncertain. Shortness of breath was elevated at 50-199 *:* g/L in West Bengal (Mazumder et al.2000), and an ecologic study in the U.S. found mortality was increased from chronic airways obstruction and emphysema at levels as low as 5-10 *:* g/L, with the highest risk at >20 *:* g/L (Engel and Smith 1994). This latter finding suggests the possibility that communities with somewhat higher arsenic concentrations in drinking water (e.g., >20 *:* g/L) may also include a higher proportion of smokers. Two concerns are: first, that smoking could be a confounder, and second, that smoking and arsenic could have synergistic effects. Since smoking acts synergistically with arsenic in producing lung cancer (Hertz-Picciotto et al.1992), a similar interaction for non-malignant respiratory diseases is possible. Although smoking is a voluntary risk, smokers do constitute a susceptible subgroup.

2.2.2.5 Reproductive effects (see table VII, Appendix 2.2).

Few reproductive endpoints have been examined in more than one study. Most of the spontaneous abortion studies were conducted in populations with high exposures; those that were not did not have individual data on confounders, and hence little confidence can be placed in the results. The time trend analyses by Hopenhayn-Rich et al.(2000) suggest that stillbirths and postneonatal mortality are increased at high exposures but not at levels between 40 and 70 *:* g/L; the decline in rates in the exposed region after arsenic levels are reduced may be partially attributable to other improvements in water quality and standard of living. In contrast, an effect on birthweight may be seen at lower levels, based on the studies to date. Transfer of arsenic to the fetus has been shown; interestingly, blood plasma arsenic was essentially all in the form of DMA, and pregnant women had a higher proportion of their urinary arsenic as DMA than nonpregnant women (Concha et al.1998), suggesting more efficient methylation during pregnancy.

2.2.2.6 Neurologic and Neurodevelopmental Endpoints (see table VIII, Appendix 2.2).

There have been studies indicating associations between environmental exposures and pathologies, symptoms, and developmental deficit.

2.2. 3 Valuation of Non-Quantified Health Endpoints

The preceding discussion suggests that some health endpoints affected by arsenic exposure, including skin cancer and ischemic heart disease could be quantified. That is, the expected reduction in cases could be calculated for each endpoint (possibly by age group) for each year following the reduction in exposure. If the magnitudes of these effects can be characterized, valuation should be done in the same way as for bladder and lung cancers. (See Charge Question 1.)

Two issues, however, arise: (1) Do unit values exit for all of the health endpoints that can be quantified? (2) Should valuation be done if effects cannot be quantified?

To answer the first question, unit values that measure what individuals would pay to avoid adverse health effects (Willingness-to-Pay estimates) do not exist for all health endpoints mentioned in our answer to Charge Question 2. *The Benefits and Costs of the Clean Air Act, 1990-2010* (USEPA 1999) contains a recent review of the available data for at least some of the relevant endpoints. Where only cost of illness estimates are available, they can be used but should be clearly described as providing lower bounds on true willingness to pay. (The EPA *Cost of Illness Handbook* is a recent source for cost of illness data for some relevant endpoints.)

To make economic valuation possible, it is important to express and characterize these other endpoints in terms of effects on people's activity levels and sense of well-being, as much

as possible. There is a fairly extensive body of data on the economic values of reducing days experiencing various symptoms, restricted activity days, hospitalizations, required treatments, etc. It would be difficult to use this body of data to value many of the health effects listed in Exhibit 5-1 (p. 5-4 of the arsenic economic analysis) such as hepatic enlargement, anemia, leukopenia, peripheral neuropathy, since the clinical significance and impact on individuals' activities of these effects is not clear.

To answer the second question raised above, it is not possible to value health effects that have not been quantified.

2.3 Exposure Reduction as a Benefit Category

> **Charge Question 3:** *Should reduction/elimination of **exposure** be evaluated as a separate benefits category, in addition to or in conjunction with mortality and morbidity reduction?*

Regarding Charge Question 3, the Panel believes that reductions in exposure should *not* be considered a separate category of benefits in a benefit cost analysis. The damage function approach to valuing benefits currently used by the Agency separates the measurement of the relationship between exposure and response (e.g., risk of fatal or non-fatal cancer) from the valuation of reductions in risk of death or illness. Epidemiologists estimate dose-response functions and economists measure the value people place on reductions in risk of death or illness. Reductions in exposure are already valued under the damage function approach when people value the reductions in the risk of death or illness associated with them. To add a separate value for reductions in exposure *per se* would be double counting.

One might argue that if some benefits from reducing arsenic exposure have not been quantified (or monetized), then an additional value should be added for reductions in exposure *per se*. There is, however, no practical way of doing this. Extending the set of health endpoints in terms of mortality and morbidity effects that can be quantified in some way (as we recommend in our answer to Charge Question 2) is the appropriate basis for developing a more complete benefit analysis, not attaching an ad hoc value to reductions in exposure.

It might be argued that EPA should abandon the damage function approach to valuing health benefits and ask people to value reductions in exposure directly. This, however, seems unwise. To abandon the damage function approach and ask people to value reductions in exposure directly would force lay people to act as epidemiologists, and there is evidence that this is difficult. Malmfors et al. (19XX) have shown that lay people do not view risk of death or illness as related to the size of the dose of a toxic substance received; any dose, however small, poses an equivalent risk. This is consistent with other studies that show that people attach a premium to reducing risks of adverse outcomes to zero (Viscusi et al., 19XY). The essence of modern risk assessment is, however, to relate health outcomes to the size of the dose received.

2.4 Comparison of Benefits and Costs

Charge Question 4: *How should total benefits and costs and incremental benefits and costs be addressed in analyzing regulatory alternatives to ensure appropriate consideration by decision makers and the public?*

2.4.1 Comparison of Benefits and Costs by System Size

One noteworthy feature of the arsenic in drinking water problem is that for the most part, those who would receive the health benefits from reductions in the concentrations of arsenic in drinking water will also bear the costs of achieving them. These costs will take the form of higher rates and prices for water supply and/or higher taxes to cover these costs. Thus it is important to try to determine whether those who receive these benefits would be willing to bear the costs of reducing arsenic concentrations in their drinking water. This is the question that benefit-cost analysis attempts to answer, because in principle the benefits of a program are defined as the sum of the affected individuals' willingness to pay for these improvements. If all benefits and costs of a regulation are measured accurately, and if benefits are less than costs, this is a signal that if the people receiving the benefits had to pay these costs, they would consider themselves to be made worse off. Conversely, if benefits exceed costs, the policy would make them better off.

For this reason, we recommend that benefits and costs should be calculated on a water supply system basis. Because of both the variability of costs and benefits across systems and the non-linearities in how benefits and costs vary with alternative regulatory standards, aggregation can produce inaccurate results. Therefore, rather than calculating the total benefits across all affected systems and the total costs across all affected systems, and then using these aggregate results to calculate total net benefits, marginal benefits, marginal costs and marginal net benefits, we recommend that total benefits, costs and net benefits and marginal benefits, costs and net benefits should be calculated for each system that is affected by the standard, and the system-level results should then be aggregated to the national level.

While there are too many affected systems to perform a separate cost analysis tailored to the specific circumstances of every system, nevertheless the existing cost analysis appears to be too generic and too little tailored to the specific circumstances of the particular utilities affected by arsenic regulation (e.g., water supply systems in the west and southwest that use groundwater). Rather than using national cost functions, an attempt should be made to employ cost functions tailored to these affected utilities. Grouping utilities into size classes and conducting an analysis by size class is acceptable if this is done with specific reference to size classes that are meaningful for the systems affected by the arsenic regulation and using data specific to these systems. In the existing analysis, individual cost analyses were only performed for water utilities that serve more than a million people ("very large systems"); we recommend lowering the threshold population size for performing individual cost analyses, for example to a service population of 250,000 or more.

2.5 Incorporation of Uncertainty into Benefits Measures

Charge Question 5: *How should uncertainties be addressed in the analysis to ensure appropriate consideration by decision makers and the public?*

Benefit-cost analyses of drinking water regulations are likely to entail uncertainties in the (a) measurement of exposure, (b) measurement of dose-response, (c) valuation of health outcomes and (d) measurement of costs. The sources of these uncertainties include measurement error (uncertainty about the average level of arsenic in tap water or of the amount of tap water consumed) as well as uncertainty about which model to use in describing the relationship between exposure and response at low doses. In general, there are two approaches to handling these sources of uncertainty—sensitivity analysis and Monte Carlo simulation. In a sensitivity analysis various assumptions are made about the correct model (e.g., dose response function) or parameter (e.g., discount rate) to use in the analysis and results are presented for each set of assumptions. In a Monte Carlo analysis a distribution is assumed for a key parameter or set of parameters (e.g., the Value of a Statistical Life) and several hundred draws are made from this distribution. Benefits are calculated for each value of the parameters drawn. This yields a probability distribution of benefits, whose parameters (e.g., the 10^{th} and 90^{th} percentiles) can be reported.

We believe that, in the case of model uncertainty, it is appropriate to rely on sensitivity analysis; however, the assumptions underlying each sensitivity analysis should be clearly spelled out when presenting results. It is particularly inappropriate to present only the highest and lowest numbers associated with a set of sensitivity analyses, which may give the reader the false impression that these constitute the upper and lower bounds of a uniform distribution. For parameters for which it is possible to specify a distribution, Monte Carlo analysis is desirable (for example, in the case of the Value of a Statistical Life).

The EPA analysis of the Arsenic in Drinking Water Rule discusses some of the sources of uncertainty in benefit estimates and handles them by performing sensitivity analyses. Specifically, it focuses on the impact of alternate assumptions about the parameters of the dose-response function, which will vary depending on what fraction of arsenic in the Taiwanese population (the population used to estimate the dose response function) is assumed to come from drinking water. A "high" and "low" estimate of benefits are generated based on alternate assumptions about the sources of arsenic exposure in Taiwan.

The other set of sensitivity analyses that are performed pertain to the Value of a Statistical Life (VSL). This is varied to allow for (a) changes in the VSL as incomes grow, (b) the involuntary nature of drinking water risks and (c) the length of the latency period. As we explain in more detail in the next section, latency (or, more correctly, the cessation lag between reduction in exposure and reduction in risk) is not handled correctly in the arsenic benefits analysis. We also have criticisms of the treatment of adjustments for income growth and for the involuntary nature of drinking water risks. *In principle*, however, there is nothing wrong with handling these sources of uncertainty through a sensitivity analysis. The choice of discount rate is also correctly handled via sensitivity analysis.

The report could, however, improve in its reporting of the results of these sensitivity analyses in two ways. First, the presentation of the details of the analysis in the Executive Summary and in the body of the report does not provide a sufficiently clear description of the specific details of all aspects of the uncertainty analysis. With considerable effort it is possible to develop a more complete understanding of how the analysis was undertaken by studying the appendices to the report. Second, when the results of two alternate assumptions are presented, for example, the "high" and "low" benefit estimates in the Executive Summary, it is important to state that these are *not* the endpoints of a uniform distribution.

3. GENERAL COMMENTS ON THE ECONOMIC ANALYSIS

3.1 Comments on Exposure Assessment

3.1.1 Overstatement of Reductions in Exposure

The benefits analysis is based on an assumption that the mean concentrations of arsenic will be 80% of the MCL. The argument is that systems will design treatment to meet an 80% standard so as to assure that realized concentrations will "never" exceed the MCL. This kind of overdesign is apparently standard practice in the drinking water industry. However, since the "overdesign" is to assure that the realized concentrations of arsenic do not exceed the MCL, the expectation that realized concentrations will at least sometimes exceed 80% of the MCL should be reflected in the exposure analysis. To the extent that the mean concentration of arsenic is greater than 80% of the MCL, benefits will be overstated. It is necessary to make an estimate of the mean concentration actually realized at each MCL.

3.1.2 Characterization of U.S. Population Exposure in the Analysis

There are a few opportunities to improve the presentation of arsenic exposures in the benefits analysis. First, although the report gives national estimates of the proportion of water systems of various types that exceed various average arsenic levels, and Tables III.C-5 and C-6 give helpful breakdowns by geographic region and the system size (population served per system), there does not appear to be an accessible presentation of the national or regional numbers of people or population aggregate exposures (people exposed X : g/liter X years/years of system operation) broken down in the same ways. A breakdown of the numbers of people in these categories is important for understanding the distributional burdens of both current arsenic exposures/health harm and the prospective compliance costs. A breakdown of the amounts of population aggregate exposure in these categories is very important for understanding the extent to which the national aggregate arsenic-in-drinking water problem would be reduced by different MCLs.

3.2 Comments on the Computation of Benefits

3.2.1 Treatment of 'Latency'

As the answer to Charge Question 1 implies, we do not believe that the lag between reduction in exposure and reduction in fatal cancers has been treated correctly in the benefits analysis. The correct approach is to predict the number of fatal cancers avoided each year based on an assumption about the percent of the steady-state reduction in cancer cases that will be achieved each year following the policy. For example, in *The Benefits and Costs of the Clean Air Act, 1990-2010*, it was assumed that 25% of the steady state benefits from reducing air pollution would be achieved in the first year of the policy, 50% by the second year, and (increasing gradually), 100% of the benefits by the end of the 5th year of the policy.

Once this time path is established, the number of fatal cancers avoided in year t should be multiplied by the Value of a Statistical Life in year t and the result discounted to the first year of the policy. The sum of these present discounted values over the horizon of the analysis yields the present discounted value of benefits of the policy. It is, of course, possible to annualize this number by calculating the constant annual value of benefits that produces the same present discounted value of benefits.

In its primary analysis the Agency makes no adjustment for the cessation lag in its calculation of cancer mortalities avoided. It simply assumes that the cancer mortality risk will drop immediately to the new steady state level upon implementation of the new standard. Then in a sensitivity analysis (Section 5.5), it accounts for the cessation lag not with alternative calculations of cancer mortalities avoided, but by discounting the Value of A Statistical Life applied to these avoided deaths for three alternative lag periods, 5, 10, and 20 years. In terms of the calculated monetary benefits, this is equivalent to assuming there is no reduction in cancer mortalities avoided for the first 5, 10, 20 years after the regulation is implemented, after which the cancer mortality risk drops immediately to the new steady state level.

3.2.2 Treatment of Age

There is sufficient information in the dose-response function in Morales et al. (2000) to calculate cancer cases avoided by age group. We believe that this should be done. The dose-response function used to compute the number of cancer cases avoided in the benefits analysis (Model 1 of Morales et al.) is a special case of equation (1) in which "the relative risk of mortality at any time is assumed to increase exponentially with a linear function of dose and a quadratic function of age (p. B-7)." Instead of using this equation to predict risks by age group, the information contained in the equation is aggregated to compute a lifetime cancer risk.

3.2.3 Valuing Avoided Cancer Mortality

(1) The Agency should recognize the uncertainty in the estimated VSL used to value fatal cancers either by sensitivity analysis or incorporating the uncertainty in Monte Carlo analyses.

(2) The committee does not believe that the adjustments to the VSL for income growth and the voluntaries/controllability of risk are entirely correct.

The arsenic benefits analysis uses elasticities of 0.22 and 1.0 as lower and upper bounds (p. 5-31) to adjust the Value of a Statistical Life for income growth. It cites EPA (2000c), claiming it is a review of the literature on elasticities and establishes the 0.22 - 1.0 as the best range. But EPA 2000c is the "Guidelines," and there is nothing in the guidelines about adjusting for income or suggesting specific elasticities. The citation is incorrect. In addition, *The Benefits and Costs of the Clean Air Act, 1990-2010* (USEPA 1999), which was reviewed by the Council for Clean Air Act Compliance and Analysis, used 0.08, 0.40, and 1.0 as low, central, and high estimates.

Regarding the adjustments for voluntariness/controllability of risk, the SAB Review of the EPA's White Paper, *Valuing the Benefits of Fatal Cancer Risk Reductions* recommended that no such adjustments be made.

3.2.4 Valuing Avoided Cancer Morbidity

With respect to nonfatal bladder cancers, an alternative to using the value for chronic bronchitis used in the Section 812 analyses is to use the value for nonfatal lymphoma obtained by Magat, Viscusi, and Huber (1996). This value is $3.6 million (in 1999$). This value was derived from a mall intercept survey, rather than a random sample of the U.S. population. But the end point being valued more closely corresponds to nonfatal bladder cancer than does chronic bronchitis. Estimates of avoided non-fatal cancers should be computed in the same fashion as estimates of avoided fatal cancers. The length of the cessation lag should also be treated in a parallel fashion.

3.3 Comments on the Computation of Costs

3.3.1 Factors that May Cause Costs to Be Overstated

Two features of the existing cost analysis may lead it to overstate the costs of arsenic regulation, at least to some degree: We recommend, that the Agency attempt to take account of these factors. (1) To the extent that arsenic removal is a joint product of water treatment together with the removal of other contaminants, the existing cost analysis may overstate the costs (or understate the benefits) of arsenic regulation. Utilities may already have pre-existing installed treatment processes for other contaminants that lower the cost of arsenic removal in a manner not reflected in the current analysis, or utilities may adopt new treatment processes in response to arsenic regulation that yield other improvements in drinking water quality as a by-product. (2) In two of three cases, the existing cost analyses for the very large systems affected by the arsenic regulations note that the costs may be overstated because they do not account for options that may be available to lower costs associated with ground water entry points: "Depending on the spatial distribution of the wells, it may be possible to implement centralized treatment, with reduced compliance costs. It may also be possible to achieve compliance without treatment by blending ground water with surface water. Finally, depending on the additional capacity available from surface water and unaffected well, the city could shut down affected wells." Presumably, the same considerations apply to some of the other systems affected by arsenic regulation.

3.3.2 Amortization of Costs

In the arsenic benefits analysis capital costs are amortized (expressed as annual equivalent flows) by using a discount rate of 7%. An alternative calculation based on a 3% rate is also presented. However, what matters for the impact on utility finances and utility customers is the actual interest rate at which the affected utilities will finance these investments. We

recommend that the Agency estimate this when calculating the regulatory costs (Freeman, Measurement ..., 1993, pp. 213-216; Kolb and Schemata, JPAM, 1990).

Exhibit 6-7 of the arsenic economic analysis presents data showing recommended cost of capital estimates for various types of water utility ranging from 4.17% to 5.94%. Having reviewed the report from which they derive, we do not believe these estimates are adequate. First, while the analysis allows for the use of different sources of capital by non-small utilities of different sizes (those serving 10,001 - 50,000 and those serving over 50,000) it assumes that the costs of various types of capital – long-term debt, short-term debt, equity capital, municipal bonds – are the *same* regardless of size for all systems serving over 10,000. We do not believe this assumption is likely to be accurate. Second, with investor owned utilities the report states that an after-tax figure is appropriate for the required analysis. We disagree and instead recommend (1) using a before-tax figure for the cost of capital for investor owned utilities, and (2) using a separate account to track the revenue gains to the government sector from taxes from the water system debt.

By way of illustration, suppose an investor owned water utility and a public owned water utility both need to borrow $1 million. Suppose the investor owned utility issues bonds with an interest rate of 8.5%. The publicly owned utility can borrow at a lower interest rate since the interest paid on its bonds is tax exempt; it can borrow at 5.19%, to use the figure from page 29 of the report on Public Water System Cost of Capital. The difference of 3.31% (= 8.5 - 5.1) is the savings due to the tax exemption on publicly owned system debt. The report recommends using 5.19% as the cost of capital for investor owned utility debt as well as publicly owned utility debt, because it views the 3.31% interest increment as merely a transfer payment. While this is not incorrect, it is misleading with respect to the policy implications. Because the investor owned utility pays a higher interest rate for its debt than the publicly owned utility, its customers will face a larger cost increase than those of the publicly owned utility. We believe this should be made explicit in the analysis.

Third, for similar reasons we disagree with the way in which the report treats the financing of capital costs on a pay-as-you-go basis out of current revenues or accumulated capital reserves. This type of financing accounts for about 20-30% of cost of capital expenditures for non-small systems, and 20-60% for small systems. The report imputes an opportunity cost of capital to funds from this source. For example, if a small system needs to fund $1 million of water supply improvement from cash flow, the report recommends amortizing this as though the funds were being borrowed with unrated or low rated general obligation bonds at an interest rate of 5.47%. Suppose the investment were being made over a 5-year period. If the utility had made no provision for a sinking fund, it would need to raise the $1 million from higher water rates over the 5-year period. To the extent there is a sinking fund, the impact on water rates will be less severe. It is clear, however, that using an imputed cost of capital may not give an accurate assessment of the short-term impact on water rates when financing water system investments from cash flow.

REFERENCES

Axelson O, Dahlgren E, Jansson C-D, Rehnlund SO. Arsenic exposure and mortality: a case-referent study from a Swedish copper smelter. Brit J Indus Med 1978;35:8-15.

Breslow and Day, _____1987

Enterline and Henderson, ----------1973

Chen C-J, Chiou H-Y, Chiang M-H, Lin L-J, Tai T-Y. Dose response relationship between ischemic heart disease mortality and long-term arsenic exposure. Arterioscler thromb Vasc Biol 1996;16:504-510

Chen C, Hsueh, YM, Lai, MS, Shyu, MP, Chen, SY, Wu, MM, Kuo, TL, Tai, TY. Increased prevalence of hypertension and long-term arsenic exposure. Hypertension 25:53-60(1995).

Chen C-J, Wu M-M, Lee S-S, Wang J-D, Cheng S-H,Wu H-Y. Atherogenicity and carcinogenicity of high arsenic Artesian well water. Arteriosclerosis 1988;8:452-460.

Chiou H, Wei-I, H, Che-Long, S, Shu-Feng, C, Yi-Hsiang, H, Chien-Jen ,C. Dose-response relationship between prevalence of cerebrovascular disease and ingested inorganic arsenic. Stroke 28:1717-23(1997).

Concha G, Vogler G, Lezcano D, Nermell B, Vahter M. Exposure to inorganic arsenic metabolites during early human development. Toxicological Sci 1998;44:185-190.

Engel RR, Smith AH. Arsenic in drinking water and mortality from vascular disease: an ecologic analysis in 30 counties in the United States. Arch Environ Health 1994;49:418-427.
Engel RR, Hopenhayn-Rich, Receveur O, Smith AH. Vascular effects of chronic arsenic exposure: a review. Epidemiologic Rev 1994;16:184-209.

Freeman, AM _____1993 (cited in section 3.3.2)

Gomez-Caminero A. Cardiovascular Effects of Arsenic During Pregnancy. Doctoral Dissertation, University of North Carolina, Chapel Hill, 2001.

Hertz-Picciotto I, Smith AH, Holtzman D, Lipsett M, Alexeeff G (1992) Synergism between occupational arsenic exposure and smoking in lung cancer induction. Epidemiology 3:23-31.

Hertz-Picciotto I, Arrighi HM, Hu S-W (2000). Does arsenic exposure increase the risk for circulatory disease? Amer J Epidemiol 151:174-181

Hopenhayn-Rich C, Browning SR, Hertz-Picciotto I, et al. Chronic arsenic exposure and risk of infant mortality in two areas of Chile. Environ Health Persp 2000;108:667-673.

Hsueh Y-M, Wu W-L, Huang Y-L, Chiou H-Y, Tseng C-H, Chen C-J. Low serum carotene level and increased risk of ischemic heart disease related to long-term arsenic exposure. Atherosclerosis 1998;141:249-257.

Jensen GE, Hansen ML. Occupational arsenic exposure and glycosylated haemoglobin. Analyst 1998;123:77-80.

Kolb and Schemata _____ (cited in section 3.3.2)

Lagerkvist BEA, Linderholm H, Nordberg GF. Arsenic and Raynaud's phenomenon. Int Arch Occup Environ Health 1988;60:361-364

Lagerkvist B, Linderholm H, Nordberg GF. Vasospastic tendency and Raynaud's phenomenon in smleter workers exposed to arsenic. Environ Res 1986;39:465-474.

Lai M-S, Hsueh Y-M, Chen C-J, et al. Ingested inorganic arsenic and prevalence of diabetes mellitus. Am J Epidemiol 139:484-492(1994).

Lewis, et al, _____1999

Magat, Viscusi and Huber _____ 1996

Malmfors _____19XX

Morales, et al., _____ 2000

NDWAC. Benefits Workgroup Recommendations, October, 1998.----------

Peto _____ 1995

Rahman M, Tondel M, Chowduhury IA, Axelson O. Relations between exposure to arsenic, skin lesions, and glucosuria. Occup Environ Med 1999;56:277-281.

Rahman M, Tondel, M, Ahmad, A, Chowdhury, I, Faruquee, M, Axelson, O. Hypertension and arsenic exposure in Bangladesh. Hypertension 33:74-78(1999).

Regas, Diane. Request for review of the benefits assessment for the arsenic in drinking water regulation. Memorandum from the Acting Assistant Administrator for Water, US EPA, June 8, 2001.

SAB. An SAB Report on EPA's White Paper Valuing the Benefits of Fatal Cancer Risk Reductions, EPA-SAB-EEAC-00-013, July 2000.

Thomas, ----------1983

Thomas, _____ 1987

Thomas, ---------- 1988

Tollerud _____ 1999

Tsai S-M, Wang T-N, Ko Y-C. Mortality for certain diseases in areas with high levels of arsenic in drinking water. Arch Environ Health 1999;54:186-193.

Tseng C-H, Chong C-K, Chen C-J, Tai T-Y. Dose-response relationship between peripheral vascular disease and ingested inorganic arsenic among residents in blackfoot disease endemic villages in Taiwan. Atherosclerosis 1996;120:125-33.

Tseng C-H, Tai T-Y, Chong C-K, et al. Long-term arsenic exposure and incidence of non-insulin-dependent diabetes mellitus: a cohort study in arseniasis-hyperendemic villages in Taiwan. Environ Health Persp 2000;108:846-851.

USEPA. Arsenic in Drinking Water Rule Economic Analysis. EPA 815-R-00-026, December 2000.

USEPA. *The Benefits and Costs of the Clean Air Act, 1990-2010* (USEPA 1999)

USEPA. Cost of Illness Handbook. _____

USEPA. *Guidelilnes for Preparing Economic Analyses.* EPA 240-R-00-003, September 2000a.

USEPA. National Primary Drinking Water Regulations; Arsenic and Clarifications to Compliance and New Source contaminants Monitoring: Final Rule. EPA-815-Z-01, Federal Register, Vol. 66(14)6976-7066. January 22, 2001

Viscusi, K., et al.----------

Wu M-M, Kuo T-L, Hwang Y-H, Chen C-J. Dose-response relation between arsenic concentration in well water and mortality from cancers and vascular diseases. Amer J Epidemiol 1989;130:1123-1132.

APPENDICES

APPENDIX 1 - BACKGROUND

Appendix 1.1 SAFE DRINKING WATER ACT PROVISIONS

SDWA Requirements for Setting the Standard

The Safe Drinking Water Act requires EPA to establish a Maximum Contaminant Level Goal (MCLG) and to promulgate a National Primary Drinking Water Regulation (NPDWR) if the Administrator determines that: i) the contaminant may have an adverse effect on the health of persons; ii) the contaminant is know to occur or there is substantial likelihood that the contaminant will occur with a frequency and at levels of public health concern; and in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.

The MCLG is to be set at the level at which no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety. Further, the regulation for a contaminant with an MCLG shall specify a Maximum Contaminant Level (MCL) which is as close to the MCLG as is feasible. If it is not economically or technically feasible to measure the contaminant, a treatment technique can be promulgated in lieu of an MCL.

SDWA further defines feasible to mean with the use of best technology, treatment techniques, and other means are available taking cost into consideration. And when the Administrator proposes a NPDWR she must also publish a determination as to whether the benefits of the MCL justify, or do not justify, the costs. Among other factors, this determination is to be based on the analysis an analysis of each of the following: i) quantifiable and nonquantifiable health risk reduction benefits for which there is a factual basis in the rulemaking record to conclude that such benefits are likely to occur as the result of treatment to comply with each level for the contaminant; ii) quantifiable and nonquantifiable costs for which there is a factual basis in the rulemaking record to conclude that such costs are likely to occur as a result of compliance with the MCL; iii) the incremental costs and benefits associated with each alternative MCL; iv) effects of the contaminant on the general population and groups within the population that are identified as likely to be at greater risk of adverse health effects due to exposure to contaminants in drinking water than the general population.
And v) other relevant factors, including quality/extent of information, uncertainties in the analyses above, and factors with respect to the degree and nature of the risk.

The Administrator is explicitly given the authority to establish a MCL at a level other than the feasible level, if the technology, treatment techniques, and other means used to determine the feasible level would result in an increase in the health risk from drinking water by increasing the concentration of other contaminants or interfering with the efficacy of techniques used to comply with other NPDWRs or if she determines as above that the benefits of a MCL would not justify the costs of complying with the level. In that case, the Administrator may

promulgate a MCL that maximizes health risk reduction benefits at a cost that is justified by the benefits.

Appendix 1.2 NDWAC Benefits Workgroup Recommendations, October, 1998

The National Drinking Water Advisory Council (NDWAC) was charged with providing EPA with recommendations on which benefits should be routinely considered in developing its regulations. They were to address what categories of benefits should be considered, how to consider qualitative benefits, and how to compare the results of benefits assessments with cost analyses. NDWAC adopted the following recommendations from the Working Group:

Recommendation 1: EPA should focus its benefits analysis efforts primarily on assessing effects on human health, defining these effects as clearly as possible and using the best available data to value them. It is also recommended that EPA consider 1) health risk reductions, 2) taste and odor improvements, 3) reduction in water system materials damage, 4) commercial water treatment cost reductions, 5) benefits due to source water protection, and 6) benefits derived from the provision of information on drinking water quality.

Recommendation 2: EPA should devote substantial efforts to better understanding the health effects of drinking water contaminants, including the types of effects, their severity and affected sensitive subpopulations. Better information is also needed on exposures and the effects of different exposure levels, particularly for contaminants with threshold effects. These efforts should pay particular attention to obtaining improved information concerning impacts on children and other sensitive populations.

Recommendation 3: EPA should clearly identify and describe the uncertainties in the benefits and costs analysis, including descriptions of factors that may lead the analysis to significantly understate or overstate total benefits and costs. Factors that may have significant but indeterminate effects on the benefits and costs estimates should also be described.

Recommendation 4: EPA should consider both quantified and non-quantified benefits in regulatory decision making. The information about quantified and non-quantified (qualitative) benefits should be presented together in a format, such as a table, to ensure that decision-makers consider both kinds of information.

Recommendation 5: EPA should consider incremental benefits and costs, total benefits and costs, the distribution of benefits and costs, and cost-effectiveness in regulatory decision-making. This information should be presented together in a format, such as a table, to ensure its consideration by decision-makers.

Recommendation 6: Whenever EPA considers regulation of a drinking water contaminant, it should evaluate and consider, along with water treatment requirements to remove a contaminant, source water protection options to prevent such contaminant from occurring. The full range of benefits of those options should be considered.

APPENDIX 2

Appendix 2.1 Supplemental Information to Charge Question 1

Estimates of latency can be approached by developing classical Armitage-Doll multi-stage models of the morbidity and mortality from various cancers in the U.S. population and then exploring mathematically the expected distributions of times to diagnosis and death from various cancers, making various plausible assumptions about where arsenic might act in the sequence of genetic changes leading to the different cancers. Recent (1994-98) U.S. morbidity and mortality data for different cancers are available from the "SEER" program [Ries, L. A. G., Eisner, M. P., Kosary, C. L. Hankey, B. F., Miller, B. A., Clegg, L., and Edwards, B. K. (2001) SEER Cancer Statistics Review, 1973-1998, National Cancer Institute, Bethesda, Md.].

The most straightforward approach to specifying the models is to do a simple set of weighted regression analyses to these data of the form:

Log(Incidence or Mortality Rate in cases/100,000 population per year) = k*Log(Age – L) + b

In this equation, L is a lag period that represents the typical time between the unobserved birth of the first cancer cell and either cancer diagnosis or cancer death (for morbidity v. mortality data, respectively), and k + 1 is the number of "stages" (sequential genetic changes) in the cancer model. Some fits derived from the data from Taiwan are contained in Attachment A. The "U.S. incidence data" worksheet contains SEER incidence and mortality data for lung and bladder cancer for each sex, but the model fitting has not yet been done. The "5-stage male smoker" worksheet shows an example of a 5-stage lung cancer model created several years ago to represent the expected time pattern of development of lung cancer in smokers who began smoking at age 13. [See Hattis, D., and Silver, K. "Use of Mechanistic Data in Occupational Health Risk Assessment--The Example of Diesel Particulates," in Chemical Risk Assessment and Occupational Health--Current Applications, Limitations, and Future Prospects, C. Mark Smith, David C. Christiani, and Karl T. Kelsey, eds., Greenwood Publishing Group, Inc., Westport CT, 1994, pp. 167-177 for an example of prior use of this approach]

Such a model makes it straightforward to explore the implications of different assumptions about which stages are affected by arsenic exposures. Additional data available in the literature may help judge the relative likelihood of different stage-of-action assumptions. In addition to the Chen et al. (1991) paper cited above, the following by Tsai et al. (1998) might be useful in estimating the rates at which risks for various health effects might decrease when exposure is decreased [Tsai, SM, Wang, TN, and Ko, YC Cancer mortality trends in a blackfoot disease endemic community of Taiwan following water source replacement. J. Toxicol Environ. Health 55(6):389-404 1998]. It is important that the estimate the latent benefits from lowering exposure to individuals that have had prior arsenic exposure be estimated utilizing the same model utilized to estimate potency. Mode of action has implications for how rapidly and completely the effects in the exposed population are reversed as it does when exposure increases to increase the risk of cancer. Thus, it is important to be consistent in the utilization of mode of action information in the final treatment of risks.

As indicated above, in the ideal circumstance there needs to be some consideration or at least acknowledgment of the different ages at the time the rule is put into effect. Benefits will accrue over a lifetime for children conceived after treatment is instituted. However, at that moment there will be people of different ages who will gain some benefit. Benefits to these individuals could be significantly larger if arsenic were largely a late stage carcinogen. This appears to be the basis of the reduction in lifetime risks associated with discontinuation of smoking even after several years. Arsenic produces a variety of effects at the molecular and cellular level that can contribute to cancer risk. It is probable that there will be insufficient data to come to hard conclusions about how different modes of action are contributing to the cancer incidence at different doses or dose rates. Because the experimental data (i.e. mechanistic data) that is available today indicate the possibility of several distinctly different modes of action with different metabolic forms of arsenic at different doses such an exercise will be viewed as being highly speculative by scientists. Thus, unless more certainty can be brought to the analysis than was apparent in the Panel's brief review of the literature, it is suggested that such analyses be confined to the uncertainty analysis as it has the distinct possibility of confusing the more straightforward derivation of latency information from existing data. It is strongly suggested that the sophistication of the methodology applied be limited by and consistent with recommendations of the National Research Council (NRC) panel, which has been charged with making recommendations on the risk assessment methodology that should be used.

APPENDIX 2.2

Supplement to Charge Question 2

Studies addressing the major categories of concern at lower exposure levels are listed in the tables (which are not comprehensive, but rather, representative). These studies demonstrate a broad array of related endpoints and indicate the range and weight of evidence, qualitatively, as well as the consistency with which these effects are related to arsenic exposure. Such consistency, particularly when at least some of the studies are of high quality and have adjusted for individual-level confounders, strengthens the evidence for causality.

I. Human morbidity studies of cardiovascular endpoints

Outcome	Authors/year & location	Design	Exposure assessment	Dose-response analysis:	Measure of association	Range of exposures
Cerebrovascular disease/cerebral infarction	Chiou et al 1997 Taiwan	Retrospective cohort	Cumulative exposure Avg concentr'n in H_2O	Significant; adjusted for age, sex, cigarettes, alcohol	Odds ratio	<0.1, 0.1-4.9, ≥5.0 mg/L-year; <0.1, 0.1-50, 50.1-2999.9, ≥300 ug/L
Ischemic heart disease	Hsueh et al 1998 Taiwan	Retrospective cohort	Duration of exposure via H_2O	Significant, adjusted for total cholesterol, BMI, hypertension, serum α– and β-carotene	Odds ratio	<13, 13-29, ≥30 years drinking artesian well water
Electrocardio-graphic abnormalities	Ohnishi et al 2000 Japan	Prospective, patients with promyelocytic leukemia	As Tx for promyelocytic leukemia	Prolonged QT intervals in all 8 patients, serious arrhythmias in 4	--	15 mg/kg for 20-79 days
Hypertension	Chen et al 1995 Taiwan	Retrospective cohort	Cumulative exposure [Avg conc in H_2O]*	Significant; adjusted for age, sex, diabetes, proteinuria, BMI	Odds ratio	0, 0.1-6.3, 6.4-10.8, 10.9-14.7 mg/L-years; 0, .01-.70, >.70 mg/L
"	Rahman et al 1999 Bangladesh	Retrospective cohort	Cumulative exposure Avg concentr'n in H_2O	Significant; adjusted for age, sex, BMI	Prevalence ratio	0, <1.0, 1.0-5.0, >5.0-10.0 mg/L-years; <0.5, 0.5 to 1.0, >1.0 mg/L
Systolic blood pressure	Jensen & Hansen 1998 Denmark	Retrospective cohort	Job with arsenic exposure, urinary As		Difference in means	Mean of 22.3 nmol/mmol As in creatinine vs. 12.0 nmol/mmol for referents
Vasospastic tendency (finger systolic pressure,	Lagerkvist et al 1986 Sweden	X-sectional	Urinary As available but not used- Estimated exposure at 300 ug/day, or 4 g over 23 years	No dose-response analysis conducted	Difference in prevalence	10-340 ug/L (mean=70) in urine among exposed; 5-20 ug/L among referents, highest quartile had mean of 180 ug/L

upon cooling)						

I. Human morbidity studies of cardiovascular endpoints (con't)

Outcome	Authors/year & location	Design	Exposure assessment	Dose-response analysis:	Measure of association	Range of exposures
Blackfoot disease**	Chen et al 1988 Taiwan	Retrospective cohort	Duration of exposure via H_2O			0 (referent) 1-29, ≥30 years drinking artesian well water
Peripheral vascular disease***	Tseng et al 1996 Taiwan	Retrospective cohort	Cumulative exposure Duration well water use Duration living in Bf area	Significant in highest exposure group, adjusted for age, sex, BMI, cigarette smoking, diabetes hypertension, serum total cholesterol, & triglycerides	Odds ratio	0 (referent), 0.1-19.9, ≥20 mg/L-years 0, 1-19, 20-29, ≥30 years drinking artesian well water
Raynaud phenomenon, numbness & other symptoms	Lagerkvist et al 1988 Sweden	Time trend – start to end of vacation		No dose-response analysis conducted. Significant difference in numbness & other signs,	Difference in prevalence	Exposed: mean of 61 ug/L urine
von Willebrand factor	Gomez-Caminero 2001 Chile	Prospective cohort of pregnant women	Exposed vs. unexposed town	Significant vs. referents	Difference in means, odds ratio for lowest tertile	<2 ug/L (referent), ~45 ug/L (exposed)

* The analysis for this exposure metric did not adjust for all factors in the next column

** Blackfoot disease has been used as an indicator of exposure to arsenic &/or susceptibility to the effects of arsenic, due to its close association with elevated arsenic exposures.

***Diagnosed by Doppler ultrasound, ABI<0.9 on either side of extremity

II. Human mortality studies of cardiovascular & renal endpoints

Outcome	Authors/year & location	Design	Exposure assessment	Dose-response analysis:	Measure of association	Range of exposures
Circulatory disease	Tsai et al 1999 Taiwan	Retrospective cohort, 1971-1994	Townships with arsenic contaminated water from 1900's to mid-1970's	Significant in both sexes, adjusted for age, calendar year	Standardized mortality ratio	0.78 ppm, referents: local county, and national rates
"	Hertz-Picciotto et al, 2000 US smelter workers	Retrospective cohort	Cumulative occupational exposure over the worklife	Significant dose response adjusted for age, year of hire, and the healthy worker survivor effect	Rate ratio	<750 (referent), 750-1999, 2000-3999, 4000-7999, 8000-19,999, ≥20,000 ug/m^3 –years
Cardiovascular disease	Wu et al 1989 Taiwan	Retrospective cohort 1973-1986	Villages with arsenic contaminated water	Significant, adjusted for age, sex	Mortality ratio	<0.3, 0.3-0.59, ≥.60 ppm
"	Axelson et al 1978 Sweden, area around smelter	Case-control	Employment in exposed jobs	Significant dose response	Mantel-Haenszel rate ratio	Not employed at smelter (referent), employed at smelter: 'close to' 0.5 mg/m^3
"	Hertz-Picciotto et al, 2000 US smelter workers	Retrospective cohort	Cumulative occupational exposure over the worklife	Significant dose response adjusted for age, year of hire, and the healthy worker survivor effect	Rate ratio	<750 (referent), 750-1999, 2000-3999, 4000-7999, 8000-19,999, ≥20,000 ug/m^3 –years
Ischemic heart Disease	Chen et al 1996 Taiwan	Two prospective cohorts, 1985-1993, and 1988-1995	Avg concentr'n in H_2O Cumulative exposure	Monotonic dose response, models adjusted for age, sex, baseline BMI, cigarette smoking, serum cholesterol, triglycerides, diabetes, hypertension, blackfoot disease*	Hazard ratio from Cox proportional hazards model	0 (referent), 0.1-9.9, 10.0-19.9, 20.0+ mg/L years
"	Tsai et al 1999 Taiwan	Retrospective cohort, 1971-1994	Townships with arsenic contaminated water from 1900's to mid-1970's	Significant in both sexes, adjusted for age, calendar year	Standardized mortality ratio	0.78 ppm, referents: local county, and national rates
Hypertensive heart disease	Lewis et al 1999 Utah, USA	Retrospective cohort	Cumulative exposure. Means in towns ranged	Significant excess in men and women	Standardized mortality	<1, 1-4.999, ≥5.0 ppm-years,

			from 18.1-164.4 ppb		ratio	range

II. Human mortality studies of cardiovascular & renal endpoints (con't)

Outcome	Authors/year & location	Design	Exposure assessment	Dose-response analysis:	Measure of association	Range of exposures
Cerebrovascular disease	Wu et al 1989 Taiwan	Retrospective cohort 1973-1986	Villages with arsenic contaminated water	Significant, adjusted for age, sex	Mortality ratio	<0.3, 0.3-0.59, ≥.60 ppm
"	Tsai et al 1999 Taiwan	Retrospective cohort, 1971-1994	Townships with arsenic contaminated water from 1900's to mid-1970's	Significant in both sexes, adjusted for age, calendar year	Standardized mortality ratio	0.78 ppm, referents: local county, and national rates
Peripheral vascular disease	Wu et al 1989 Taiwan	Retrospective cohort 1973-1986	Concentr'n in H in villages with arsenic contaminated water	Significant, adjusted for age, sex	Mortality ratio	<0.3, 0.3-0.59, ≥.60 ppm
"	Tsai et al 1999 Taiwan	Retrospective cohort, 1971-1994	Townships with arsenic contaminated water from 1900's to mid-1970's	No dose measure used, adjusted for age, sex, calendar year	Standardized mortality ratio	0.78 ppm, referents: local county, and national rates
"	Engel & Smith 1994 USA	Ecologic study at the county level	Avg concentr'n in H_2O	No clear monotonic dose response, but elevated risk at each level >5 ug/L	Standardized mortality ratio	5-10, 10-20, >20 ug/L
Pulmonary heart disease	Tsai et al 1999 Taiwan	Retrospective cohort, 1971-1994	Townships with arsenic contaminated water from 1900's to mid-1970's	No dose measure used, adjusted for age, sex, calendar year	Standardized mortality ratio	0.78 ppm, referents: local county, and national rates
**	Engel et al 1994					
Nephritis, nephrosis	Tsai et al 1999 Taiwan	Retrospective cohort, 1971-1994	Townships with arsenic contaminated water from 1900's to mid-1970's	No dose measure used, adjusted for age, sex, calendar year	Standardized mortality ratio	0.78 ppm, referents: local county, and national rates
"	Lewis et al 1999 Utah, USA	Retrospective cohort	Cumulative exposure. Means in towns ranged from 18.1-164.4 ppb	Significant excess in men and women	Standardized mortality ratio	<1, 1-4.999, ≥5.0 ppm-years, range

*Adjustment for Blackfoot disease attenuated but did not eliminate the association of arsenic exposure with ISHD

**For further mortality and morbidity studies of cardiovascular endpoints, see Table 6, Engel et al., 1994.

III. Animal morbidity studies of cardiovascular endpoints

Outcome	Authors/year	Design	Exposure assessment	Dose-response analysis adjusted for:	Measure of association	Exposure level
Animal Studies						
Vasoreactivity	Bekemeir & Hirschelmann 1989	Experiment	Not applicable – controlled dosing	Only one dose group		15 mg/kg, orally
Vasoreactivity	Carmignano et al 1983	Experiment	"	Only one dose group		50 ug/mL drinking water
Potentiation of β-adrenoreceptor stimulation	"		"	Only one dose group		
Stroke volume, cardiac output	Carmignano et al 1985	Experiment	"	Only one dose group		50 ug/mL drinking water
Vasoreactivity *			"	Only one dose group		

* after administration of isoprenaline, clonidine, tyramine, etc.

IV. Human mortality and morbidity studies of endocrinologic/metabolic conditions and biomarkers

Outcome	Authors/year & location	Design	Exposure assessment	Dose-response analysis:	Measure of association	Range of exposures
Diabetes mellitus mortality	Tsai et al 1999 Taiwan	Retrospective cohort, 1971-1994	Townships with arsenic contaminated water from 1900's to mid-1970's	No dose measure used, adjusted for age, sex, calendar year	Standardized mortality ratio	0.78 ppm, referents: local county, and national rates
Diabetes mellitus incidence	Lai et al 1994 Taiwan	Retrospective cohort	Cumulative exposure Duration well water use*	Significant, adjusted for age, sex, BMI, physical activity	Odds ratio	0 (referent), 0.1-15.0, ≥15.1 ppm-yrs; 0 (referent, 1-10, 11-20, ≥21 years drinking artesian well water
"	Rahman et al 1996 Sweden	Retrospective cohort	Job in glassworks with likely exposure	Significant in those with highest exposure, adjusted for age	Odds ratio	No quantitation available
"	Tseng et al 2000 Taiwan	Prospective cohort, ~2.5 years follow-up	Cumulative exposure from H_2O	Significant, adjusted for age, sex, BMI	Hazard ratio from Cox model	<17 mg/L years (referent), ≥17 mg/L years
Glycosylated hemoglobin	Jensen & Hansen 1998 Denmark	Retrospective cohort	Jobs with arsenic exposure (taxidermists, construction workers, wood & electric pylon impregnators	Significant vs. referents	Difference in medians	6-44 nmol/mmol urinary As in creatinine (referents); 12-295 nmol/mmol (exposed)
"	Gomez-Caminero 2001 Chile	Prospective cohort of pregnant women	Exposed vs. unexposed town	Significant vs. referents	Difference in means, odds ratio for >6.5%	<2 ug/L (referent), ~45 ug/L (exposed)
Glucosuria	Rahman et al 1999 Bangladesh	Retrospective cohort	Avg concentr'n in H_2O Cumulative exposure	Significant, adjusted for age and sex, using cumulative exposure	Prevalence ratio	<0.5, 0.5-1.0, >1.0 mg/L; <1.0, 1.0-5.0, >5.0-10.0, >10.0 mg/L-years
Hepatic function: bilirubin excretion, ALP activity	Hernandez-Zavala et al 1998 Mexico	Retrospective cohort	Mean water concentration in each of three towns	Significant differences, adjusted for age, alcohol, tobacco, pesticides	Difference in means	Means: 14.0 ug/L (referent), 116 ug/L and 239 ug/L in two exposed towns

* The analysis for this exposure metric did not adjust for all factors in the next column

V. Human studies of cancers other than lung and bladder

Outcome	Authors/year & location	Design	Exposure assessment	Dose-response analysis:	Measure of association	Range of exposures
Kidney cancer	Smith et al 1992 Taiwan	Retrospective cohort	Cumulative exposure in H_2O	Significant, adjusted for age, sex	Rate ratio	
Liver cancer	" →	" →	" →	" →	" →	"
Prostate cancer	Tsai et al 1999 Taiwan	Retrospective cohort 1971-1994	Townships with arsenic contaminated water from 1900's to mid-1970's	Adjusted for age, sex, calendar year	Standardized mortality ratio	0.78 ppm, referents: local county, and national rates
"	Lewis et al 1999 Utah, USA	Retrospective cohort	Cumulative exposure. Means in towns ranged from 18.1-164.4 ppb	Significant excess	Standardized mortality ratio	<1, 1-4.999, ≥5.0 ppm-years, range
Stomach cancer*	Tsai et al 1999 Taiwan	Retrospective cohort 1971-1994	Townships with arsenic contaminated water from 1900's to mid-1970's	Adjusted for age, sex, calendar year	Standardized mortality ratio	0.78 ppm, referents: local county, and national rates
Colon cancer*	" →	" →	" →	" →	" →	"
Rectum cancer*	" →	" →	" →	" →	" →	"
Liver cancer*	" →	" →	" →	" →	" →	"
Nasal cancer*	" →	" →	" →	" →	" →	"
Laryngeal ca*	" →	" →	" →	" →	" →	"
Skin cancer*	" →	" →	" →	" →	" →	"
Bone cancer*	" →	" →	" →	" →	" →	"
Lymphoma*	" →	" →	" →	" →	" →	"

*Excess observed in both genders. Cancers found in excess in only one gender not included.

VI. Human morbidity & mortality studies of non-malignant respiratory endpoints

Outcome	Authors/year & location	Design	Exposure assessment	Dose-response analysis:	Measure of association	Range of exposures
Respiratory effects: cough, shortness of breath	Mazumder et al 2000 West Bengal, India	X-sectional	Current concentration measured in well water	Significant, adjusted for age & sex, smokers excluded	Prevalence odds ratio	<50, 50-199, 200-499, 500-799, ≥800 ug/L
Bronchitis	Tsai et al 1999 Taiwan	Retrospective cohort 1971-1994	Townships with arsenic contaminated water from 1900's to mid-1970's	Adjusted for age, sex, calendar year	Standardized mortality ratio	0.78 ppm, referents: local county, and national rates
Chronic airways obstruction	Engel & Smith 1994 USA	Ecologic study at county level	Avg concentr'n in H_2O	Adjusted for age, sex, and calendar year	Standardized mortality ratio	5-10, 10-20, >20 ug/L
Emphysema	" →	" →	" →	" →	" →	"

VII. Human reproductive studies

Outcome	Authors/year & location	Design	Exposure assessment	Dose-response analysis:	Measure of association	Range of exposures
Spontaneous abortion	Nordstrom et al 1978 Sweden	Retrospective cohort of pregnancies	Residential proximity to a smelter	Trend in frequency by distance of region to smelter	Prevalence ratio	No quantitation
"	Nordstrom et al 1979 Sweden	Retrospective cohort of pregnancies	Employment in smelter prior to or during pregnancy	Highest prevalence among those living near the smelter during or after their employment	Prevalence ratio	"
"	Borzsonyi et al 1992 Hungary	Retrospective cohort	Concentration in H_2O	Significant difference comparing high vs. low arsenic region	Prevalence rate difference	Low (not quantitated referent), 170-330 ug/L
"	Ahmad et al 2001 Bangladesh	Retrospective cohort of pregnancies	Concentration in H_2O Duration of residence in high arsenic area	Significant difference comparing high vs. low arsenic region, and for those with longer duration	Prevalence rate difference	<20 (referent), >100 ug/L
"	Aschengrau et al 1989 Massachussetts	Case-control	Concentration in H_2O	Trend in risk	Odds ratio	<0.8, 0.8-1.3, 1.4-1.9 ug/L
Stillbirth	" →	" →	" →	" →	" →	"
"	Borzsonyi et al 1992 Hungary	Retrospective cohort	Concentration in H_2O	Significant difference comparing high vs. low arsenic region	Prevalence rate difference	Low (not quantitated referent), 170-330 ug/L
"	Hopenhayn-Rich et al 2000 Chile	Retrospective vital statistics	Concentration in H_2O Comparison of two communities	Significant difference during period when exposures were very high	Mortality rate difference and ratio	<5 (referent), various levels to >800 ug/L
Preterm birth	Ahmad et al 2001 Bangladesh	Retrospective cohort of pregnancies	Concentration in H_2O Duration of residence in high arsenic area	Significant difference comparing high vs. low arsenic region, and for those with longer duration	Prevalence rate difference	<20 (referent), >100 ug/L

VII. Human reproductive studies (con't)

Outcome	Authors/year & location	Design	Exposure assessment	Dose-response analysis:	Measure of association	Range of exposures
Birthweight	Nordstrom et al 1978 Sweden	Retrospective cohort of pregnancies	Residential proximity to smelter or employment	Lowest birthweight among those living nearest the smelter	Difference in birthweight	No quantitation
Low birthweight	Hopenhayn et al 2001 Chile	Prospective cohort & review of vital statistics	Concentration in H_2O Comparison of two communities	Significantly increased risk of low birth weight	Odds ratio for low birthweight	<2 (referent), 40-50 ug/L
Congenital malformations	Nordstrom et al 1979 Sweden	Retrospective cohort of pregnancies	Employment in the smelter	Higher prevalence of congenital malformations among employed mothers	Prevalence ratio	"
Coarctation of the aorta	Zierler et al 1988 Massachussetts	Case-control	Routine monitoring of water	Above vs. below the limit of detection, three-fold increased risk, adjusted for seven other contaminants, source of water, maternal education	Odds ratio	< limit of detection (0.8 ug/L), >limit of detection
Neonatal mortality	Hopenhayn-Rich et al 2000 Chile	Retrospective vital statistics	Concentration in H_2O Comparison of two communities	Significant difference during period when exposures were very high	Mortality rate difference and ratio	<5 (referent), various levels to >800 ug/L
Postneonatal mortality	" →	" →	" →	" →	"→	"

VIII. Human studies of neurologic and neurodevelopmental endpoints

Outcome	Authors/year & location	Design	Exposure assessment	Dose-response analysis:	Measure of association	Range of exposures
Peripheral neuropathy	Gerr et al 2000 Georgia, USA	Cross-sectional	Dust & soil arsenic measurements	Significant trend, adjusted for age, education, sex, verbal intellectual score, alcohol	Odds ratio	House dust: 1-1200 ug/g Window sill dust: 0.5-192 Attic dust 1.2-2635 ug/g Soil 2.0-1845 ug/g
Various neurobehavioral parameters*	" →	" →	" →	" →	Linear regression	"
Verbal IQ	Calderon et al 2001 Mexico	Cross-sectional	Urinary arsenic	Significant inverse correlation	Partial correlation coefficient	<50, 50-100, >100 ug As/g creatinine; Range: 27.5-186.2 ug/g creatinine

*Vibrotactile threshold, standing steadiness, tremor intensity

A Public Health Based Approach to Calculating the Magnitude of Unquantified Health Effects

Several of the analyses of the health effects of arsenic in Taiwan use Standardized Mortality Ratios (SMRs) to compare death rates in villages with high levels of arsenic in drinking water to death rates in unexposed areas. The analysis below compares the number of excess deaths due to lung and bladder cancers (based on SMRs) with excess deaths due to other cancers and due to vascular disease. The goal is to compare the magnitude of excess deaths for endpoints for which dose-response has not been quantified to excess deaths for endpoints for which dose-response functions exist. This suggests the possible magnitude of effects that might be established if dose-response functions were estimated.

The spreadsheet in Attachment 1 to Appendix 2.2, performs this analysis using data reported in Wu et al. (1989) and Tsai et al (1999). For the Wu et al. data the basic findings are that (1) cancers other than lung and bladder have similar aggregate excess deaths as the sum of lung plus bladder cancer excess deaths, and (2) vascular deaths are comparable in number to the sum of lung plus bladder cancer excess deaths. This suggests that the total mortality effect at the high exposure levels in the Wu et al. study is about three times the effect of the previously quantified lung and bladder cancers. For the Tsai et al. data, the basic findings are similar for total excess cancer deaths—about double those from lung plus bladder cancer by themselves. However, the vascular excess deaths for these data are just over half the excess deaths from lung plus bladder cancers. This

apparent difference from the Wu et al. results may be related to the fact that more of the Tsai et al. data are from a somewhat later period relative to the end of exposure than the earlier Wu et al. data. One possible interpretation of this is that the vascular deaths may tend to have a shorter average lag time relative to exposures than the cancer deaths.

Wu, M. M., Kuo, T. L., Hwang, Y. H., and Chen, C. J. Dose-response relation between arsenic concentration in well water and mortality from cancers and vascular diseases. Am J. Epidemiology 130:1123-1132

Numbers of Deaths (Table 2)								From Tables 3 and 4						
Mortality from 1973-1986			**Numbers of Deaths**					**Age-Adjusted Mortality Per 100,000**						**Excess Dea**
		Males			Females			Males			Females			Males
	< .3 ppm	.3-.59 ppm	= .6 ppm	< .3 ppm	.3-.59 ppm	= .6 ppm	< .3 ppm	.3-.59 ppm	= .6 ppm	< .3 ppm	.3-.59 ppm	= .6 ppm		.3-.59 ppm
Cancers														
All sites	*243*	*244*	*150*	*191*	*180*	*144*	*224.56*	*405.12*	*534.61*	*162.22*	*277.2*	*487.2*		*180.56*
Bladder	23	36	26	30	36	30	22.64	61.02	92.71	25.6	57.02	111.3		38.38
Kidney	9	11	6	4	13	16	8.42	18.9	25.26	3.42	19.42	57.98		10.48
Skin	2	8	9	2	10	5	2.03	14.01	32.41	1.73	14.75	18.66		11.98
Lung	53	62	32	43	40	38	49.16	100.67	104.08	36.71	60.82	122.16		51.51
Liver	54	42	27	25	16	10	47.78	67.62	86.73	21.4	24.18	31.75		19.84
Prostate	1	5	3				0.95	9	9.18					8.05
Leukemia	6	4	1	4	3		4.87	6.52	2.69	3.03	4.55	0.00		1.65
Nasopharynx	4	5	2	2	4	1	3.58	8.16	8.58	1.59	5.81	4.89		4.58
Esophagus	8	5	2	2	2		7.62	9.37	6.55	1.83	3.64	0.00		1.75
Stomach	26	10	10	8	11	2	25.66	17.82	56.42	6.71	18.72	5.98		-7.84
Colon	8	6	3	11	5	5	7.94	8.3	12.51	9.05	8.16	17.21		0.36
Uterine Cervix				1	4	1				0.91	5.46	3.92		0
Unidentified sites	49	50	29	59	36	36	43.91	83.73	97.49	50.24	54.67	113.35		39.82
Vascular Diseases														
All vascular diseases	*363*	*230*	*136*	*320*	*226*	*93*	*364.1*	*421.47*	*572.68*	*277.5*	*370.79*	*386.41*		*57.37*
Peripheral vascular diseases	21	29	14	21	29	8	22.54	57.8	60.4	18.2	48.00	35.82		35.26
Cardiovascular diseases	127	85	62	105	93	37	125.87	153.98	259.51	91.14	153.07	144.74		28.11
Cerebrovascular accidents	137	81	44	106	60	30	137.8	145.36	175.72	92.42	98.11	120.68		7.56
Unidentified vascular disease	78	35	16	88	44	18	77.89	64.33	77.05	75.74	71.61	85.17		-13.56

Data from

Tsai, S. M., Wang, T. N., and Ko, Y. C. Mortality for certain diseases in areas with high levels of arsenic in drinking water. Arch. Environmental Health 54:186-193 (1999).

All mortality data are for 1971-1994--after nearly all phase-out of the arsenic in drinking water exposure in the mid-1970's

Expected deaths are for the local comparison group

		Numbers of Deaths for Men								**Numbers of Deaths for Women**				
	Observed	Expected	SMR	95% LCL SMR	95% UCL SMR	Excess Deaths	Ratio to Lung + Bladder Ca		Observed	Expected	SMR	95% LCL SMR	95% UCL SMR	Excess Deaths
All Causes	***11193***	***8265.758***	***1.32***	***1.29***	***1.35***	***2927***	***3.90***		***8875***	***6329.72***	***1.4***	***1.37***	***1.43***	***2545***
Cancers														
All sites	*2774*	*1263.95*	*2.19*	*2.11*	*2.28*	*1510*	***2.01***		*2029*	*843.9*	*2.4*	*2.3*	*2.51*	*1185*
Oral	23	20				3	0.00		12	7.46				5
Pharyngeal, except NPC	24	17.75				6	0.01		10	4.24	2.36	1.13	4.34	6
Nasopharyngeal	60	50.59				9	0.01		29	31.13				-2
Esophagus	69	41.2	1.67	1.3	2.12	28	0.04		12	7.59				4
Stomach	195	143.84	1.36	1.17	1.46	51	0.07		111	79.46	1.4	1.15	1.68	32
Intestine	15	7.15				8	0.01		8	5.81				2
Colon	91	61.05				30	0.04		83	58.47	1.42	1.13	1.76	25
Rectum	46	31.96				14	0.02		33	21.98	1.5	1.03	2.11	11
Liver	631	345.27	1.83	1.69	1.98	286	0.38		224	119.28	1.88	1.64	2.14	105
Gallbladder	13	11.68				1	0.00		11	12.18				-1
Pancreas	30	24.57				5	0.01		19	19.75				-1
Nasal	40	13.3	3	2.14	4.09	27	0.04		29	5.82	4.98	3.33	7.15	23
Laryngeal	30	16.81	1.78	1.2	2.55	13	0.02		13	2.73	4.76	2.53	8.15	10
Lung	699	225.39	3.1	2.88	3.34	474	0.63		471	114.02	4.13	3.77	4.52	357
Bone	41	16.64	2.46	1.77	3.34	24	0.03		34	15.11	2.25	1.56	3.14	19
Skin	66	13.65	4.83	3.74	6.15	52	0.07		68	11.96	5.68	4.41	7.21	56
Breast									47	46.48				1
Cervical									122	96.09	1.27	1.05	1.52	26
Ovary									15	13.78				1
Prostate	48	19.07	2.52	1.86	3.34	29	0.04							
Bladder	312	34.99	8.92	7.96	9.96	277	0.37		295	20.96	14.07	12.51	15.78	274
Kidney	94	13.91	6.76	5.46	8.27	80	0.11		128	14.4	8.89	7.42	10.57	114
Brain	19	15.03	1.26	0.76	1.97	4	0.01		21	11.99	1.75	1.08	2.68	9
Lymphoma	56	34.4	1.63	1.23	2.11	22	0.03		35	20.57	1.7	1.18	2.37	14
Leukemia	67	50.07	1.34	1.04	1.7	17	0.02		40	37.36				3
Diabetes mellitus	188	139.69	1.35	1.16	1.55	48	0.06		343	221.72	1.55	1.39	1.72	121